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Familial melanoma risk genes in Queensland

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Abstract

Melanoma 'risk' is multifaceted, with genetic, phenotypic, and environmental factors all contributing to melanoma predisposition. Although the majority of melanoma is attributable to random acquired mutations in melanocytes, a positive family history is associated with an increased risk of developing the disease, and the presence of heritable germline variants is an important component of melanoma susceptibility for some families. Mutation in one of the known high penetrance melanoma predisposition genes, comprising *CDKN2A, CDK4, BAP1, POT1, ACD, TERF2IP,* and *TERT*, underpins melanoma risk for approximately half of all high-density familial clustering of melanoma. However, the underlying genetic basis of disease remains unexplained for many families.

It is likely that a polygenic component to melanoma predisposition accounts for the remainder of families, where overall susceptibility is influenced by combinations of low to moderate risk polymorphisms, rare high penetrance germline mutations, and modulation of risk by environmental and genetic factors. Although no single presently known germline alteration guarantees disease development, the main impact of predisposition genes is the elevation of baseline melanoma risk. For an individual with existing genetic susceptibility, it is likely that fewer sporadic mutations are required to accumulate before a critical level for oncogenesis is reached. Beyond conferring risk of cutaneous melanoma, some ‘melanoma’ predisposition genes have been linked to diverse cancer phenotypes. Familial risk has been proposed as a shared feature of many cancers, and clustering of additional cancers in melanoma families has been observed at rates greater than expected by chance.

In a cohort of 178 'intermediate risk' melanoma families, cancer development was assessed over a 33 year period, and identified significantly more than expected bladder cancer, lymphoid leukaemia, and myeloma. Further to population level cancer risk, it is proposed that some cancer dense families carry known and possibly as-yet-unidentified melanoma predisposition genes.

Eight families with high melanoma case density and eleven individuals with three or more invasive cancer types including melanoma were selected for further follow up with whole exome or whole genome sequencing. Multiple damaging variants in cancer-associated genes were identified, supporting a polygenic basis for melanoma susceptibility. Given the diversity of genetic variants and other cancer types in the cohort, it is possible that some cancer-associated genes identified here also have pleiotropic effects in predisposing to melanoma.

Declaration by author

This thesis is composed of my original work, and contains no material previously published or written by another person except where due reference has been made in the text. I have clearly stated the contribution by others to jointly-authored works that I have included in my thesis.

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Publications during candidature

Peer-reviewed papers

Read J, Wadt K, Hayward N. Melanoma Genetics. J Med Genet. 2016;53:1-16.
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– incorporated as Chapter 2.

Contributor	Statement of contribution
Dr Jazlyn Read (Candidate)	Wrote the paper (80%) Designed and created figures 1, 4, and 5 (100%) Composed figures 2 and 3 from images supplied by Dr K Wadt
Prof Nicholas K Hayward	Reviewed and edited all drafts of paper (20%)
Dr Karin Wadt	Sourced clinical photographs used in figure 2 and figure 3, viewed final manuscript
Dr Matthew Law	Statistical analysis of low penetrance risk loci in Table 1
Dr Kiarash Khosrotehrani	Assisted with the descriptions of dermoscopic features for figures 2 and 3.

Contributions by others to the thesis

Prof Nicholas K Hayward: significant contribution to conception and design of the project, and critical review of work at all stages of the thesis.

Ms Judith Symmons: sourcing death information and pathology results at the Queensland Cancer Registry.

Ms Jane Palmer: assistance and advice with the pedigree program Progeny and for locating some historical consent forms and pathology results at QIMR Berghofer. Partial follow up of five melanoma families.

Dr Peter Johansson: annotation of variants included in Chapter 4.

Researchers involved in the Queensland Familial Melanoma Project: initial recruitment of the families included in this thesis in 1982, and follow up until approximately 2005.

Statement of parts of the thesis submitted to qualify for the award of another degree

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It seems surreal that the nights after work and weekends spent poring over pedigrees and pathology, analysing data, and writing late into the night are drawing to a close.

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Keywords

cancer, familial, genetics, hereditary, melanoma, polygenic, skin, risk

Australian and New Zealand Standard Research Classifications (ANZSRC)

ANZSRC code: 111203, Cancer genetics, 100%

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FoR code: 1112, Oncology and carcinogenesis, 100%

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List of Abbreviations used in the thesis

AML:	acute myeloid leukaemia
CLL:	chronic lymphocytic leukaemia
CML:	chronic myeloid leukaemia
CRC:	colorectal cancer
FDR:	first degree relative
NHL:	non-Hodgkin lymphoma
PolyPhen2:	Polymorphism Phenotyping v2
Q-MEGA:	Queensland Study of Melanoma: environmental and genetic associations
QIMR Berghofer:	The QIMR Berghofer Medical Research Institute
QFMP:	Queensland Familial Melanoma Project
RCC:	renal cell carcinoma
SIFT:	Sorting Intolerant from Tolerant
WES:	whole exome sequencing
WGS:	whole genome sequencing
WT:	wild type

Chapter 1

Introduction

This project aims to assess melanoma risk genes and development of other cancers in a population based sample of Queensland melanoma cases and their families. The study cohort comprises 178 families originally ascertained as part of the Queensland Familial Melanoma Project (QFMP), designated as 'intermediate risk' due to confirmed primary melanoma in two first-degree relatives, diagnosed between 1982 and 1990. Of the 'intermediate risk' group, these 178 families had not had further contact since a follow up study (The Queensland Study of Melanoma: environmental and genetic associations (Q-MEGA)) was completed between 2002 and 2005, when one or more individuals in each family answered a telephone interview relating to personal and family cancer information.

Follow up was conducted of these 178 families to determine all new occurrences of melanoma and other cancers, as validated by Queensland Cancer Registry and pathology records. Testing of existing saliva DNA samples enabled genetic analysis of the families, with further exome sequencing for families with a high melanoma case density and overall cancer burden.

Known high penetrance mutations predisposing to melanoma account for only approximately half of all familial clustering, and it is hypothesised that a number of other high penetrance risk genes exist. Additionally, since some 'melanoma' risk genes are associated with the development of other cancers, it is hypothesised that other novel high-penetrance melanoma risk genes also predispose to other cancer types. Therefore this study aims to address the specific hypotheses that:

1. Known melanoma predisposition genes are associated with the development of melanoma in a cohort of 'intermediate' risk families, i.e. those of relatively low case density.
2. Novel high-penetrance germline melanoma genes associated with development of melanoma have yet to be identified.
3. Some high-penetrance melanoma genes are associated with the development of other cancers.
4. Additional cancer types may be over-represented in 'melanoma' families due to underlying predisposition to cancer conferred by multiple low penetrance alleles and environmental modifiers.

Chapter 2

Familial melanoma genetics and links with other cancers

Read J, Wadt K, Hayward N. Melanoma Genetics. J Med Genet. 2016;53:1-16.

Relevance to thesis aims

This chapter relates to all four thesis aims, by exploring the existing genetic landscape of familial melanoma and also seeking to identify new genes in the literature that may be associated with melanoma development. For thesis aim 1, this chapter discusses known melanoma predisposition genes, and relates to thesis aim 2 by exploring novel research evidence and putative melanoma predisposition genes, enabling these genes of interest to be prioritised during the next generation sequencing stage of the project. A focus on additional cancers linked to 'melanoma' predisposition genes and review of low to moderate penetrance alleles relate to aims 3 and 4 respectively.

This chapter was initially prepared and written with the intention of it forming the first chapter of the thesis, and subsequently was submitted for publication. It represents an overview of familial melanoma, existing links with other cancers, and a polygenic basis of disease that 'sets the scene' for detailed exploration of these topics in a cohort of melanoma families.

Contribution of candidate

I prepared the manuscript and all figures and tables. I created figures 1, 4, and 5 in Microsoft powerpoint, and composed figures 2 and 3 from supplied clinical photographs.

Acknowledgement of the contribution of others

Supervisor Prof Nicholas Hayward reviewed and edited all draft versions of the manuscript. Dr Karin Wadt sourced clinical photographs used in figure 2 and figure 3, and supplied comments on the final manuscript. Dr Kiarash Khosrotehrani kindly assisted with the descriptions of dermoscopic features for figures 2 and 3. Dr Matthew Law conducted statistical analysis of low penetrance risk loci in Table 1.

INTRODUCTION

The concept of melanoma risk is dynamic and multi-faceted, owing to the diverse aetiology and heterogeneous nature of the disease. Genetic, phenotypic, and environmental risk factors all contribute to melanoma predisposition. The majority of alterations underlying the genetic basis of this disease occur as random acquired mutations within melanocytes, and an accumulation of genomic changes contribute to melanoma development, progression, and evolution. However, the presence of heritable germline variants is an important component of melanoma susceptibility.[1] Genes that predispose to melanoma are typically grouped into low, medium, and high penetrance genes.[2] Penetrance relates to the likelihood of a mutation carrier developing the disease over time, and reflects the overall contribution of a specific gene polymorphism, or mutation, to melanoma risk. Although no single presently known germline alteration guarantees melanoma development, the main impact of predisposition genes is the elevation of baseline melanoma risk. For an individual with moderate to high genetic susceptibility, it is likely that fewer somatic mutations are required to accumulate before a critical level for oncogenesis is reached. Additionally, melanoma risk genes may interact directly with other genes or environmental risk factors to influence and activate melanoma growth pathways.[1, 3]

A positive family history is associated with an increased risk of developing melanoma, and is particularly significant when there is a first-degree relative with multiple primary melanomas, or single primary melanomas in two or more first-degree relatives.[1] The most common gene implicated in familial melanoma is cyclin-dependent kinase inhibitor 2A (*CDKN2A*), accounting for predisposition in approximately 20-40% of melanoma families.[1] Despite a handful of other known high penetrance genes, many cases of familial melanoma are not accounted for molecularly, and the genetic basis for susceptibility remains unexplained for a large percentage of families. This suggests a likely polygenic mechanism of inheritance, including multiple low-risk alleles and genetic modifiers, as well as the possibility of rare mutations in other high-penetrance genes yet to be discovered. The risk genes that underpin familial melanoma may also be relevant to other cancers. Familial clustering of additional cancers has been observed in melanoma families, particularly pancreatic cancer linked to *CDKN2A* mutations, and the evidence for melanoma being part of broader cancer syndromes is mounting.[1, 4]

HIGH PENETRANCE GENES

CDKN2A

The *CDKN2A* gene on chromosome 9p21 consists of four exons that encode two unrelated proteins in different reading frames arising from alternatively spliced transcripts. p16 inhibitor of cyclin-dependent kinase 4 (p16INK4A) is produced from the alpha transcript of exons 1α, 2, and 3, whereas p14 alternate reading frame (p14ARF) is produced from the beta transcript of exons 1β, 2, and 3. The main tumour suppressor activity of p16INK4A is through inhibition of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6), thus maintaining retinoblastoma protein (RB) in a hypo-phosphorylated state to prevent cell cycle S-phase entry.[5] p14ARF is a positive regulator of p53, and therefore a loss of p14ARF allows for accumulation of DNA damage as cells escape the senescence barrier.[5] The structure of *CDKN2A* into two reading frames means that mutations can affect either p16INK4A, p14ARF, or both, depending on which exon is affected. Autosomal dominant inheritance of germline *CDKN2A* mutations has been implicated in approximately 20-40% of familial melanoma, although the mutation frequency varies between different geographic regions.[5]

Geographically-linked founder mutations have been documented, with some occurring as a single predominant mutation based on common ancestry. *CDKN2A* founder mutations have been found in Sweden and the Netherlands, namely p.Arg112dup and p16-Leiden respectively, both located in exon 2 and originating in northern Europe approximately 2000 years ago.[6] Another dominant variant has been identified in Iceland, with G89D mutation contributing to the genesis of approximately 2% of all invasive cutaneous melanoma in that country.[7] In Europe, G101W occurs as a founder mutation in France, Italy, and Spain.[5] A number of common mutations are shared between Australia and the United Kingdom, including M53I, IVS2-105A/G, R24P, and L32P, reflecting a shared ancestry from British colonisation of Australia in the late 18th century.[5] Differences in mutation penetrance between regions likely reflect a combination of genetics and environment associated factors, where family members are predicted to share the same ultraviolet radiation (UVR) exposures as well as a number of other heritable genetic modifiers.[1] Several independent features have been associated with positive *CDKN2A* mutation status, including multiple primary melanomas, high number of family members with melanoma, Breslow thickness >0.4 mm, and early age of melanoma onset.[8, 9] Compared with the relatively high penetrance in cohorts of familial melanoma, a much lower lifetime risk has been identified for individuals with *CDKN2A* mutation in population-based analysis.[10]

Amongst the high penetrance familial melanoma genes, *CDKN2A* is unique in that it has also been identified as a low penetrance gene conferring increased risk of melanoma in the general population. Genome-wide association studies (GWAS) have shown that variants located around the *CDKN2A* locus are associated not only with cutaneous melanoma, but also with naevus count and with tanning ability.[2, 11-13] Several independent variants are proposed to contribute to complex association signals in the *CDKN2A* region, and the association with melanoma risk is likely to involve multiple single nucleotide polymorphisms (SNPs).[2] These SNPs include rs869330 and rs7023329 within the *MTAP* gene, and rs1101970 in *CDKN2B-AS1* (Figure 1).[2, 14]

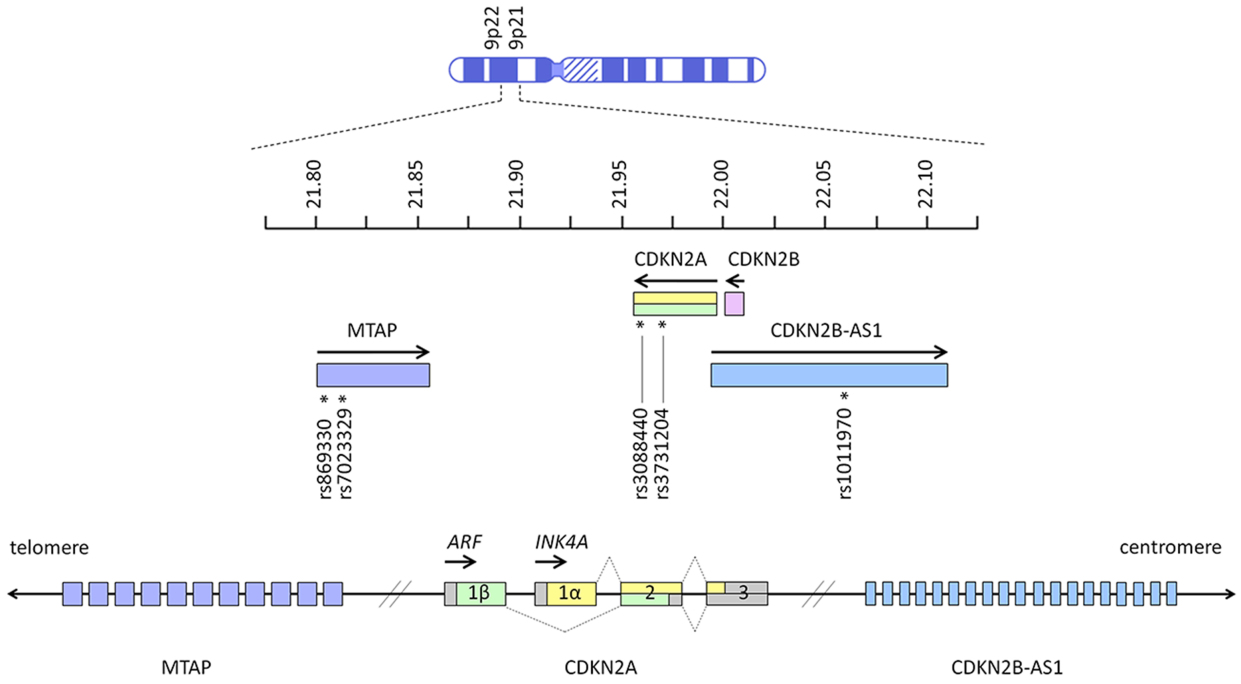

Figure 1. Recently identified single nucleotide polymorphisms on chromosome 9p21 and 9p22 in *MTAP*, *CDKN2A*, and *CDKN2B-AS1*. In *MTAP*: rs869330 at position 21804617, and rs7023329 at position 21816528; in *CDKN2A*: rs3088440 at position 21968159, and rs3731204 at position 21984661; in *CDKN2B-AS1*: rs1011970 at position 22062134.[2, 14] Arrows indicate the direction in which genes are transcribed. Units next to the chromosome ideogram indicate megabase position of each gene from the terminus of the short arm of chromosome 9. Exons (open boxes) of CDKN2A are numbered, and dotted lines show how alternative splicing generates the alternate reading frame (ARF) and INK4A gene products.

The above locus is a naevus associated region, with *CDKN2A* mutation carriers displaying a higher total naevi number and total naevi density compared with non-carriers.[15] Phenotypic naevus differences have also been observed, with mutation carriers demonstrating significantly more clinically atypical naevi (Figure 2).[15] An atypical naevus has been defined as having one or more of the following clinically observed features: size >5mm in diameter, border or contour irregularity, colour asymmetry or multiple colours, and diffusion of pigment. Some *CDKN2A* coding region mutation carriers have a clinical phenotype consistent with atypical naevus syndrome, historically also sometimes referred to as dysplastic naevus syndrome, however the variability of phenotypic expression means that not all carriers have atypical naevi.[15]

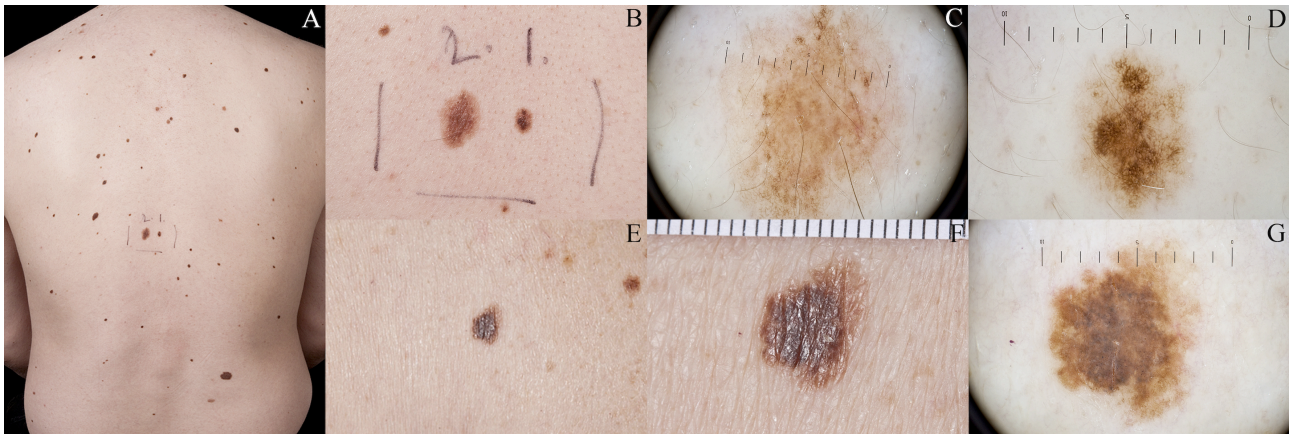

Figure 2. Atypical naevi showing the hallmarks of large size, border or contour irregularity, colour asymmetry or multiple colours, and diffusion of pigment. (A) many atypical naevi on the back; (B) close-up view of centre back naevi seen in A, showing highly irregular contour and colour variation; (C) dermoscopy of left naevus marked '2' in (A and B), demonstrating peripheral reticular distribution of pigment relatively homogeneously associated with some centrally distributed globules and pigment reinforcement. Overall the lesion is relatively symmetrical; (D) dermoscopy of right naevus marked '1' in (A and B) showing atypical reticular distribution of pigment with asymmetry in the vertical axis. Relative enlargement of pigment network in focal areas is more central with some radial streaming. Overall the lesion is relatively homogeneous in colour and does not have any blue/white veiling, regression or other hallmarks of melanoma; (E) an atypical naevus of large size, asymmetry, irregular pigmentation and contour; (F) close-up view of naevus seen in (E and G) dermoscopy of naevus seen in (E and F), showing predominantly reticular distribution of pigment with some areas of amorphous pigment. Asymmetry in the vertical axis, heterogeneous distribution of pigment and irregular borders. Multiple brown/grey dots centrally and symmetrically distributed. No blue/white veil, no regression or other hallmark of melanoma (diagnosis to be interpreted in the context of other lesions on the same patient).

CDK4

Germline mutations in *CDK4* on chromosome 12q14 impact the same pathway as *CDKN2A* mutations, and the oncogenic effects of *CDK4* mutations are primarily via the control of cell cycling in the G1 phase.[16] Two different mutations have been identified, in codon 24 of exon 2, leading to substitution of arginine with either histidine or cystine. These R24C and R24H mutations lead to CDK4 behaving as a dominant oncoprotein through loss of binding to p16, its negative regulator.[16] Thus far, a total of 18 families with *CDK4* mutations have been identified worldwide. The R24C variant has been found in six families, from France, Italy, the United Kingdom, and the United States.[16] The R24H variant has been found in the other 11 families, comprising three Latvian families, two French families, and one family each from Australia, Denmark, Greece, Italy, Norway, and the United Kingdom.[16-19] In an analysis of 17 families, median age at first melanoma diagnosis was 39 years, and the lifetime mutation penetrance based on the available data was estimated at 74%.[16] The low frequency of *CDK4* mutations means that very large population studies are required to accurately assess the contribution of *CDK4* mutations to the overall burden of familial melanoma and the penetrance of cutaneous melanoma in the context of these mutations.

BAP1

Germline inactivating mutations in BRCA1-associated protein-1 (*BAP1*), a tumour suppressor gene on chromosome 3p21, were initially identified in two distinct syndromes. Testa *et al* (2011) identified one as characterised by familial aggregation of mesothelioma and uveal melanoma, and Wiesner *et al* (2011) concurrently described the other as characterised by multiple morphologically distinct cutaneous melanocytic neoplasms and uveal melanoma.[20, 21] The familial aggregation of cancers associated with a proposed *BAP1* syndrome has subsequently been expanded to include cutaneous melanoma, and additional neoplasms are increasingly being linked to *BAP1* germline mutations, including meningioma, cholangiocarcinoma, renal cell carcinoma and basal cell carcinoma.[22-28] The diversity of cancers suggests that the inactivating mutation is variably penetrant for different tumour types, and possibly that mutations in *BAP1* depend on other unidentified genetic modifiers for a cancer phenotype to be expressed. The first recurrent *BAP1* mutation has recently been reported in three families from two continents, with one family carrying a likely independent mutation based on founder haplotype analysis.[28] A clustering of uveal and cutaneous melanoma in these families, and the presence of only one mesothelioma case, supports the hypothesis that specific *BAP1* variants predispose to certain subsets of cancers. [28]

A cutaneous phenotypic feature for *BAP1* germline mutations has been proposed by the presence of multiple 0.2-1.0 cm pink to tan papules and nodules, termed 'melanocytic *BAP1*-mutated atypical intradermal tumours' (MBAITs), or alternatively, 'BAPomas'.[21, 29-31] These lesions are similar but histopathologically distinct from atypical Spitz tumours, lacking characteristic Spitz naevi features, and are also phenotypically distinct from naevi seen in carriers of mutations in other melanoma predisposition genes such as *CDKN2A* (Figure 2 and Figure 3).[31] As these lesions typically occur at a younger age than other cancers, accurate identification could alert to the possibility of *BAP1* mutation and prompt amplified cancer surveillance. Although the MBAITs associated with *BAP1* mutations were initially reported not to progress to cutaneous melanoma, atypical features of faint orange-red pigment, red papule morphology, and halo formation have been described in cutaneous melanomas of individuals in *BAP1* mutation positive families.[23, 24, 32] The features may represent an overlap between the phenotype and cutaneous melanoma, either through transformation of an existing MBAIT, or de novo melanoma development with a phenotype influenced by the specific *BAP1* cancer pathway. Of 21 presently reported families affected by *BAP1* mutations, 16 families had at least one individual affected by cutaneous melanoma, confirming the place of melanoma in the BAP1 syndrome.[20, 22-25, 27-29, 31-35] *BAP1* functional inactivation is also proposed to contribute to a small proportion of sporadic cutaneous melanoma, with an absence of BAP1 expression on immunohistochemistry staining described in approximately 5% of tumours. [36] Therefore, in the context of familial aggregation of cutaneous melanoma, a tumour with somatic loss of 3p and/or the loss of BAP1 protein expression may suggest screening for a *BAP1* germline mutation is warranted.

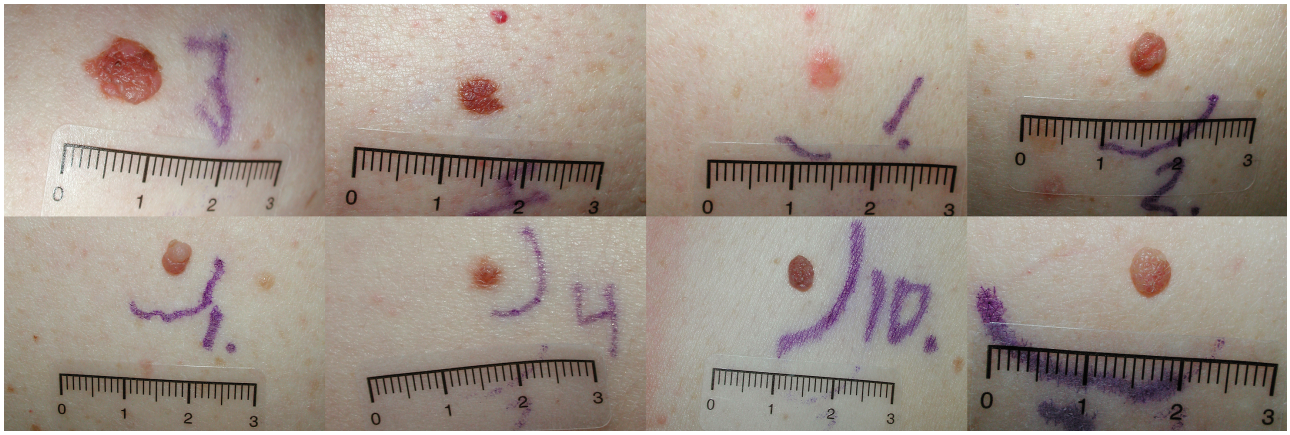

Figure 3. Examples of melanocytic BAP1-mutated atypical intradermal tumours (MBAITs)/BAPomas, demonstrating pink to tan papules and nodules, usually symmetrical in shape and of fairly uniform colour, which contrasts with the phenotype of atypical naevi (Figure 2), often seen in CDKN2A mutation carriers.

POT1

Protection of telomeres 1 (*POT1*) contributes to the six-component protein complex of shelterin, which protects telomeres by preventing them from being mistakenly recognised as deleterious DNA breaks, regulating telomere region DNA replication, as well as telomerase recruitment and activity.[37] Two recent studies have identified nine highly penetrant germline mutations in the *POT1* gene, the majority of which affect oligonucleotide/oligosaccharide-binding (OB) fold domains, which are essential for the binding of *POT1* to telomeric single stranded DNA.[37-39]

POT1 variants appear to be highly penetrant, with one study of melanoma families from the United Kingdom, the Netherlands, and Australia observing that all nine carriers developed melanoma, in addition to some individuals developing breast and small cell lung cancer.[38] Melanoma associated *POT1* mutations include a p.Tyr89Cys variant of the N-terminal OB domain in a five-case family, and a splice-acceptor variant between exons 17 and 18 in a six-case family.[38] Two further OB fold domain mutations, p.Gln94Glu and p.Arg273Leu, were each found in a case from different families.[38]

A rare novel missense variant in the OB2 domain, p.Ser270Asn, was detected in all 11 cases and obligate carriers from four Italian families, with the same variant also identified in one of two affected individuals in a bi-lineal Italian family.[39] Although all five families were apparently unrelated, the haplotype of the *POT1* region was shared by all carriers, suggesting a common ancestor approximately ten generations ago as the source of the founder mutation.[39] Two further *POT1* variants, p.Gln623His and p.Arg137His, were identified in another two Italian families.[39] In both studies, telomeres of *POT1* mutation carriers were relatively long, which has previously been identified as a risk factor for melanoma.[40]

ACD/TERF2IP

Recently, mutations in other shelterin complex genes have been found to predispose to melanoma (Figure 4). Mutations in the adrenocortical dysplasia protein homolog (*ACD*) and telomeric repeat binding factor 2 interacting protein (*TERF2IP*) genes were identified in a study of melanoma families without known genetic aetiology.[38, 39, 41] In a cohort of melanoma families that were wild-type for known predisposition genes, segregating mutations in *ACD* were found in four families, and another two mutations were identified that did not segregate with all melanoma cases in the families.[41] A nonsense mutation in one Australian family, p.Q320X, segregated in all four cases

available for genotyping, and was associated with early age at diagnosis. Another mutation, p.N249S, was identified both in an Australian family and a Danish family, with a shared founder haplotype across the *ACD* locus. In the Australian family, with eight confirmed and four unconfirmed cases of cutaneous melanoma, the mutation segregated in all seven cases available for testing. Of five confirmed and one unconfirmed case in the Danish family, three affected family members were found to be carriers. Both p.Q320X and p.N249S are within the *POT1* binding domain of *ACD*, reflecting the key role of the ACD/POT1 sub-unit in mediating the elongation of telomeres.[41]

TERF2IP is important in the negative regulation of telomere length, by repressing homology-directed repair. A nonsense mutation and three novel missense variants have been identified. The p.Q191R was associated with onset of melanoma at 15 and 24 years, and is predicted to disrupt the binding site for TERF2.[41] This loss is proposed to prevent TERF2IP contributing to the shelterin complex. A case-control analysis of the *ACD* and *TERF2IP* mutations in sporadic melanoma cases did not identify any carriers, indicating that rare mutations are likely to be significant only in a familial context.[41]

TERT

Progressive shortening of telomeres with each cell division is a characteristic of normal aging, and may be hastened by exposure to harmful environmental risks such as UVR. Maintenance of telomere length is a function of telomerase, and altered telomerase regulation contributes to the limitless replicative potential of cancer cells. Telomerase reverse transcriptase (*TERT*) encodes a catalytic subunit of telomerase, and somatic *TERT* promoter mutations have been identified in a variety of cancers, including melanoma.[42] *TERT* has also recently been implicated in familial melanoma following high-throughput sequencing of four affected and four non-affected individuals in a 14-case German family.[43] After the region was first identified by multi-point linkage analysis, sequencing of all genes in the region revealed several novel variants, including a T>G variant in the *TERT* promoter.[43] This germline mutation was found in all four affected individuals, as well as one unaffected member who was only 36 years old and had multiple naevi.[43] Two affected individuals developed melanoma at age 20 and age 30, in addition to other cancers, suggesting that this mutation is a rare but highly penetrant melanoma risk mutation. Screening of 168 cell lines from sporadic metastatic melanoma did not find other occurrences of this novel germline variant, although somatic recurrent UVR-signature mutations elsewhere in the *TERT* promoter were present in 125 of the cell lines.[43]

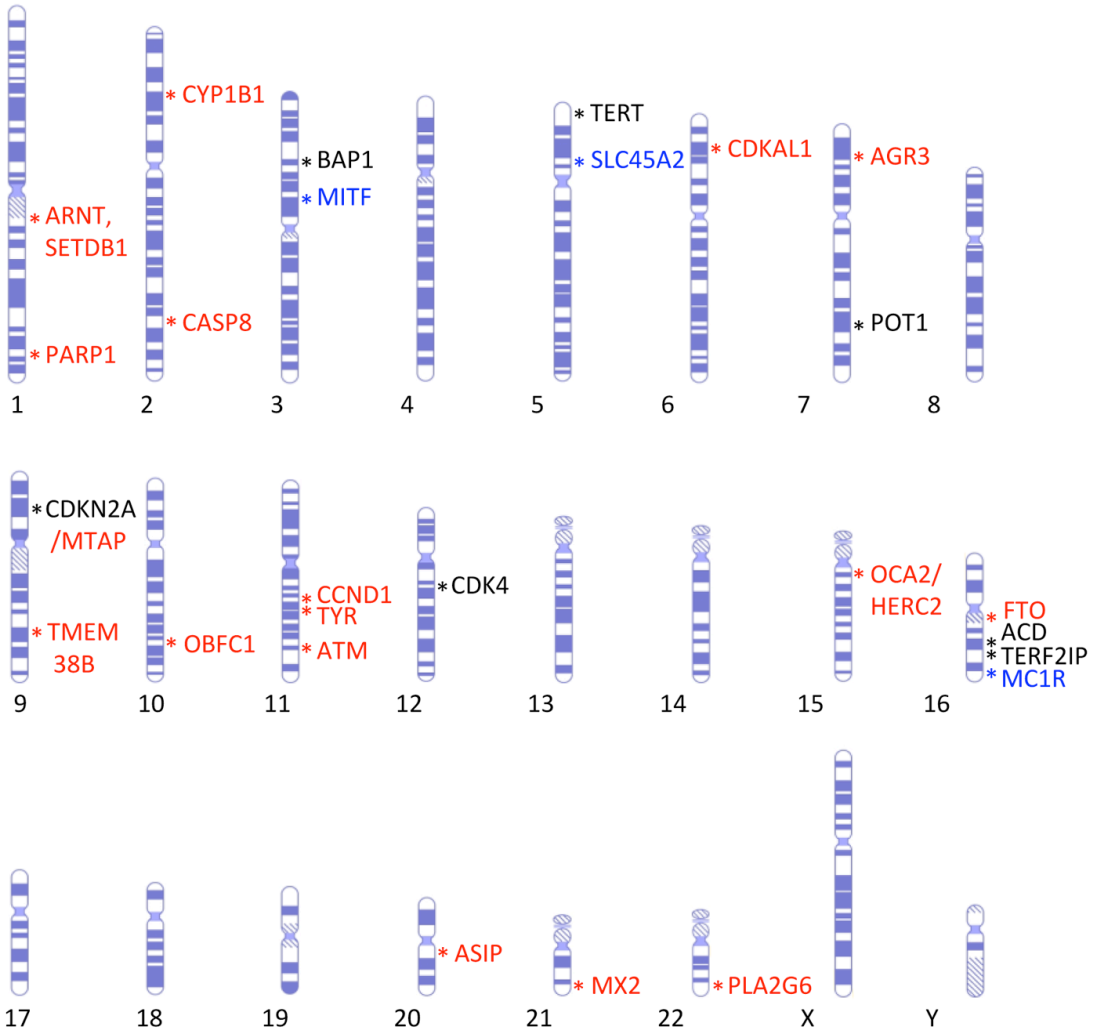

Figure 4. High, medium and low penetrance genes and their chromosome band locations. Black text denotes high penetrance genes; blue text denotes medium penetrance genes; red text denotes low penetrance genes.

MEDIUM PENETRANCE GENES

The relatively low frequency of high penetrance mutations suggests that a multitude of alternative germline mutations could help explain melanoma predisposition. Medium and low penetrance alleles are more prevalent in the general population, but singularly, they are unlikely to be enough to drive oncogenesis.[44] However, the complex interplay of several of these alleles may combine to raise the level of personal melanoma risk above a critical threshold. In this regard, a component of polygenic heritability has been demonstrated to underlie all sporadic cancers.[44] To date, three medium penetrance genes (i.e. those with variants that have odds ratios of disease association of between 2 and 5) predisposing to melanoma have been identified. Interestingly, all three are involved in natural variation in pigmentation (summarised below).

MC1R

The melanocortin 1 receptor gene (*MC1R*) encodes the G-protein coupled receptor MC1R, which binds α-melanocyte stimulating hormone (α-MSH).[45] Binding of the ligand normally activates adenylate cyclase, which then increases intracellular levels of cyclic adenosine monophosphate (cAMP). Raised cAMP triggers a subsequent cascade via downstream microphthalmia-associated transcription factor (MITF) and tyrosinase to stimulate melanocyte proliferation, dendricity, and eumelanin pigment synthesis (Figure 5).[45] The increase of photoprotective black/brown eumelanin pigments decreases the relative amount of red/yellow pheomelanins, which are poorly protective against UVR. The type and quantity of pigment determines phenotypic expression of skin and hair colour, as well as skin sensitivity to UVR and tanning response. A number of variant *MC1R* alleles associated with reduced cell surface receptor expression have been identified. This situation reduces binding of α-MSH, and subsequently lower cAMP levels result in less eumelanin and a greater proportion of pheomelanins.[45-47]

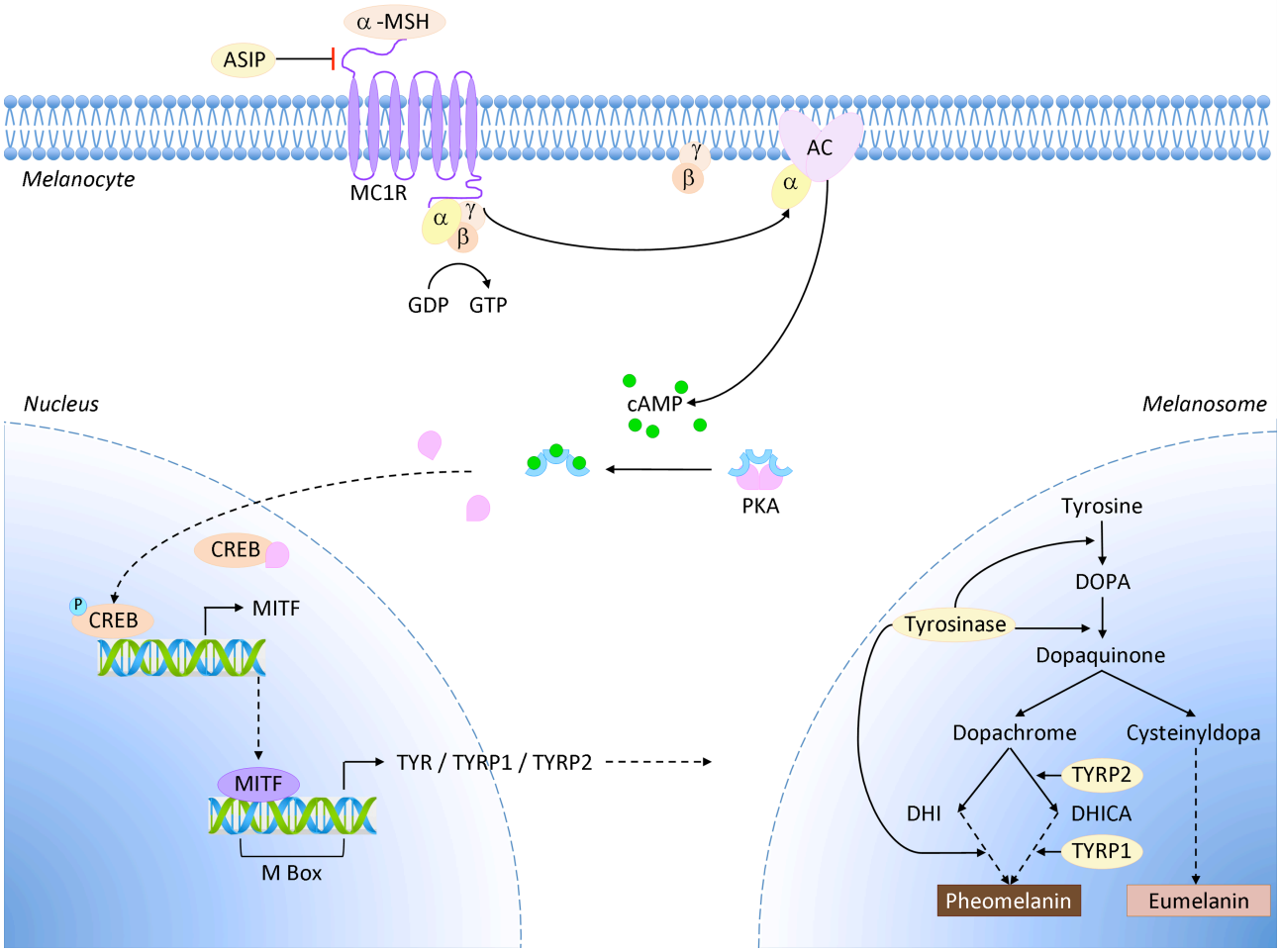

Figure 5. MC1R and the pigment synthesis pathway. Binding of α-melanocyte stimulating hormone (α-MSH) to its cognate receptor MC1R on the surface of a melanocyte triggers cyclic AMP (cAMP) production via adenylate cyclase (AC). This activates the CREB and MITF transcription factors, causing an increase in expression of several components of the melanin synthesis pathway, and leads to a switch in pigment production from pheomelanin to eumelanin in melanosomes.

MC1R is highly polymorphic and a link has been established between particular alleles and a red hair colour (RHC) phenotype. Variants most strongly associated with the RHC phenotype are termed *R* alleles, and the consequently reduced or non-functional cell surface receptors and increased pheomelanin causes the phenotypic traits of red hair colour, fair skin, freckling, and inability to tan.[45] Other *MC1R* variants that are more weakly associated with RHC and have less penetrant impact on the cell receptors are designated *r* alleles. RHC associated *MC1R* variants are typically inherited in an autosomal recessive pattern.[45] Variants may be inherited in a heterozygous +/*R* or +/*r* pattern, or a homozygous *R*/*R* or *r*/*r* state. Although red hair colour is generally a

recessive trait, increases in the percentage of individuals with fair skin, blonde hair, and red hair reflect in vitro studies of a dominant negative effect of *MC1R* variant receptors on co-inherited wild-type alleles.[45] Variants associated with melanoma include the *R* alleles D84E, R142H, R151C, R160W, and D294H, (with odds ratios of 1.85-2.90) and the *r* alleles V60L, V92M, I155T, R163Q, and T314T (with odds ratios of 1.37-2.61).[48, 49] A French case-control study recently identified 69 rare *MC1R* polymorphisms, including 25 novel melanoma predisposition variants.[48] Just over half of the identified alleles were predicted to have a functional impact (*D* variants).[48] Of the novel alleles, 14 *D* variants were exceedingly rare, each associated with only a single case in the melanoma cohort. Several others were identified in the control group.[48]

A pooled analysis with a large sample size from 17 case-control studies found that individuals carrying a single *MC1R* variant had an almost 40% increased risk of melanoma compared to homozygous wild-type controls, and that the risk attributable to any *MC1R* variant was 28%.[49] For carriers of two or more *MC1R* variant alleles, the risk of cutaneous melanoma was more than double the risk found for wild-type controls.[49] Interestingly, for individuals with the RHC phenotype, presence of *MC1R* variants alone was insufficient to independently predict melanoma risk.[49] This could possibly reflect the significant role of environment and UVR in modulating risk for RHC variant carriers.

The analysis also revealed an association between *MC1R* variants and melanoma for Caucasian patients with darkly-pigmented skin.[49] Notably, the *MC1R* variant/melanoma association has been reported as stronger for photoprotective phenotypes.[49, 50] This may reflect the putative role of *MC1R* in non-pigment pathways, including activation of nucleotide excision repair and other DNA repair mechanisms in response to UVR damage.[51-53] For variant alleles, a compromised UVR response has been attributed to a diminished α-MSH mediated oxidative stress response and reduced effects on target DNA damage response genes.[53] This link to DNA repair helps explain the role of *MC1R* in melanoma susceptibility, suggesting that variant alleles may utilise either pigment or non-pigment pathways to cause melanoma. The non-pigment pathways are particularly relevant for variants that are associated with melanoma but not with the RHC phenotype.[49]

MITF

The *MITF* gene encodes the transcription factor MITF, and is a key regulator of pigment cells, including the development and differentiation of melanocytes. A recently identified recurrent germline mutation, *MITF* p.E318K, is responsible for the substitution of glumatic acid at position 318 with lysine.[54, 55] The lysine residue at the site changes the binding affinity for a small-ubiquitin-like modifier (SUMO) protein, and subsequently decreases SUMOylation.[54, 55] SUMO directed post-translational modification typically impacts transcriptional regulators to inhibit transcription, and thus reduced SUMOylation effectively removes the brakes from MITF action on downstream targets.[56] Comparison of expression profiles for MITF regulated targets identified 37 genes, with 17 showing modest differences in expression between wild-type and p.E318K isoforms.[55] This difference may indicate that variant *MITF* mutations have particular transcriptional affinity for specific sets of target genes. Although the precise molecular mechanisms have yet to be fully elucidated, it is apparent that *MITF* p.E318K acts as a gain of function mutation predisposing to familial melanoma. Carriers of the p.E318K variant have been identified as having a significantly higher risk of developing melanoma (odds ratios of 2.09-2.19), and the p.E318K mutation has been shown to co-segregate with melanoma in multiple families.[54, 55] Co-segregation was observed in some but not all family members, implying that it is a medium-penetrance melanoma variant, similar to *MC1R*.[55] From population analysis of controls, few mutations were detected, therefore denoting *MITF* p.E318K as a rare population variant.[55, 57, 58] The p.E318K mutation has also been linked with a particular phenotype, comprising non-blue eye colour, increased number of naevi, and multiple primary melanomas.[54, 55, 57, 58]

SLC45A2

In contrast to *MC1R* and *MITF*, solute carrier family 45, member 2 (SLC45A2) variants are associated with darker skin colour, and appear strongly protective against melanoma. The gene product functions as a membrane-associated transporter protein, and is thought to influence pigmentation via the processing and trafficking of melanosomal proteins such as tyrosinase.[59, 60] The ancestral variant 374L of rs16891982 has been associated with olive and dark skin, and confers a protective effect against melanoma, even for individuals with a fair phenotype (odds ratios of 2.37-5.50).[59, 61, 62] This variant is more common in individuals from Southern Europe and the Mediterranean region, and there is a decreasing gradient of allele frequency from the south to the north of Europe.[60, 63]

LOW PENETRANCE GENES

In addition to two of the known medium penetrance genes *MC1R* and *SLC45A2*, 18 other low penetrance risk loci have been associated with melanoma through GWAS (Table 1).[64] Agouti signalling protein (*ASIP*), tyrosinase (*TYR*), tyrosinase-related protein 1 (*TYRP1*), and oculocutaneous albinism type II (*OCA2*) are involved in pigmentation.[2, 60, 61, 65] *ASIP* encodes for an antagonist of α-MSH, which competitively binds to MC1R, thereby preventing MC1R-mediated stimulation of eumelanin synthesis (Figure 5). *ASIP* has been variably associated with melanoma.[2] Similar to *MC1R* RHC variants, melanoma-associated *ASIP* SNPs have been linked to red hair and skin freckling.[66] *TYR* impacts eye colour and tanning response, where activity of the enzyme tyrosinase influences the ratio of eumelanin to pheomelanin, and thus *TYR* alterations can contribute to a fair skin phenotype (Figure 5).[66] *TYR* SNPs associated with blue eye colour and skin sun sensitivity have been significantly associated with melanoma, as have SNPs in *TYRP1*.[2, 66] *TYRP1* stabilises the protein encoded by *TYR*, and therefore mutations in this gene can also affect tanning response.[66] Further to known phenotypic associations with melanoma, increased risk has been reported for pigment related SNPs in the *HERC2*/*OCA2* region on chromosome 15q13.1.[67] The two SNPs most significantly associated with melanoma risk are rs1129038 and rs12913832, the latter being a key determinant of human blue-brown eye colour.[67, 68] *PLA2G6* is associated with both pigmentation and naevi, while *CASP8*, *TERT*, *AGR3*, *MTAP/CDKN2A*, and *FTO* are associated with variation in naevus density.[14, 61, 63, 65-67, 69-78] In addition to its role in naevus count, *TERT* is also associated with telomere length, as is *OBFC1*.[73] Two loci (*PARP1*, *ATM*) are associated with DNA repair, and two others are linked to methylthiolation of tRNA and regulation of cell cycle progression (*CDKAL1* and *CCND1* respectively).[65, 73, 79, 80] Four other loci: *ARNT/SETDB1*, *CYP1B1*, *MX2*, and *TMEM38B*/*RAD23B*, are associated with melanoma but via uncertain mechanisms.[65, 73, 79]

Table 1 Melanoma loci identified through GWAS

Gene	Chromosome band	Regional peak	OR	Pigmentation	Naevi	Refs
ARNT, SETDB1	1q21	rs12410869	0.88	No	No	79
PARP1	1q42.12	rs1858550	0.87	No	No	79, 80
CYP1B1	2p22.2	rs6750047	0.92	No	No	73
CASP8	2q33.1	rs7582362	0.89	No	Weak/Trend	65
TERT	5p15.33	rs380286	1.16	No	Yes	65, 70, 77
SLC45A2	5p13.3-13.2	rs250417	2.44	Yes, strong	No	61, 63, 65, 70, 72
CDKAL1	6p22.3	rs6914598	1.11	No	No	73
AGR3	7p21.1	rs1636744	1.11	No	Weak/Trend	73
MTAP/ CDKN2A intergenic	9p21.3	rs7852450	0.81	No	Weak/Trend	14, 65, 70, 76
(TMEM38B)	9q31.2	rs10739221	0.89	No	No	73
OBFC1	10q24.33	rs2995264	0.87	No	No	73
CCND1	11q13.3	rs498136	0.89	No	No	65
TYR	11q14.3	rs1393350	1.22	Yes, strong	No	14, 66, 69, 70
ATM	11q22.3	rs73008229	0.83	No	No	65
OCA2/ HERC2	15q12-13.1	rs4778138	0.84	Yes, strong	No	63, 67, 71-73
FTO	16q12.2	rs12596638	1.15	No	Yes	78
MC1R	16q24.3	rs75570604	1.82	Yes, strong	No	14, 68, 70
ASIP	20q11.22	rs6059655	1.42	Yes, strong	No	14, 66, 69, 70, 74, 75
MX2	21q22.3	rs408825	1.15	No	No	65
PLA2G6	22q13.1	rs2092180	0.89	Yes	Yes	14, 61, 65, 76

OR: odds ratio

GENETIC MODIFIERS AND INTERACTIONS

Overall risk in familial melanoma is modified by the pooled contribution of many factors, including other genes, phenotypic characteristics, and the environment. The addition of modifiers or interactions can influence the penetrance of a certain allele, and contribute to increased, or decreased, melanoma susceptibility.

Gene-gene

Epistasis is a gene-gene interaction, where the effect of a particular gene depends on the presence of another modifier gene. Epistasis can also be linked to multiple genes, where a certain genetic background may be essential for subsequent gene expression.[81] A number of epistatic mutations likely contribute to the polygenic inheritance of melanoma.

Further to its contribution as an independent risk gene for melanoma, *MC1R* variants act as genetic modifiers by increasing the penetrance of *CDKN2A* mutations. A recent meta-analysis showed that melanoma risk doubled for patients with mutations in both *CDKN2A* and *MC1R* compared to mutated *CDKN2A* alone, and that carriers of multiple *MC1R* variants were even more likely to develop melanoma.[3] For potential interactions of *MC1R* with other genes located near *CDKN2A*, all ten recently identified candidate polymorphisms on chromosome 9p21 did not show any significant association on interaction analysis.[11]

Telomere length has been also investigated in relation to *CDKN2A* status, following previous associations between cutaneous melanoma and longer telomeres. In contrast to non-carriers, the study failed to show a link between telomere length and melanoma for carriers of *CDKN2A* mutations, either suggesting a divergent melanoma pathway in these individuals, or more likely, insufficient power to detect an association.[40]

Interaction between the *MITF* p.E318K allele and *MC1R* RHC variants has been variably reported, and there does not appear to be an interaction in the majority of patients.[58, 82] However, one patient in an Australian cohort with a p.E318K allele and *MC1R* homozygous R/R genotype developed three amelanotic melanomas, suggesting a genetic interaction as the source of this phenotype.[58] An analysis of 33 candidate polymorphisms in several pigmentation genes and the vitamin D receptor (VDR) gene identified significant epistatic effects between *MC1R* and *TYR*, and *SLC45A2* and *VDR*, among others.[12]

MC1R has been proposed to also interact with somatic *BRAF* p.V600E mutations to drive melanomagenesis, likely by allowing cells to bypass senescence.[83] In vivo studies have demonstrated that the simultaneous expression of *BRAF* p.V600E and *MC1R* depletion results in greater melanocyte growth and tumour formation compared to either factor alone.[83]

Gene-phenotype

Pigmentation traits with less melanin are linked to melanoma via reduced protection against UVR. Phenotypic risk factors for melanoma in the general population include blue or green eyes, fair or red hair, fair skin with increased sun sensitivity and an inability to tan, high numbers of naevi, and atypical naevi. Several genetic variants predisposing to pigment and naevus phenotypes have been identified in the general population, which in turn have been implicated in predisposition to melanoma.[45] In addition to the effect on DNA repair, the variant *MC1R*-mediated RHC phenotype of red hair, pale skin, and an inability to tan confers melanoma susceptibility by increased potential for sunburn and UVR damage.[45] The medium penetrance risk gene *MITF* has been associated with the phenotypic characteristic of high naevus count.[55, 58] In an Australian study, carriers displayed significantly higher counts of naevi greater than 5 mm, but without distinct dermoscopic naevus signature patterns.[58] For carriers of the p.E318K mutation, there was an association with non-blue eye colour but no association with other known phenotypic characteristics, including skin colour, hair colour, and freckling.[55]

Gene-environment

The most significant independent environmental risk factor for melanoma is UVR exposure, and a potential interaction between geographic location and *CDKN2A* penetrance has been observed. A large international study of families from three continents found significant variation in mutation penetrance depending on geographical location, likely correlating with associated UVR exposure.[1] By age 50, mutation penetrance reached 0.13, 0.50, and 0.32 in Europe, the United States, and Australia, respectively. By age 80, it was 0.58 in Europe, 0.76 in the United States, and a staggering 0.91 in Australia.[1] Although these penetrance rates appear to correspond with latitude and hence UVR exposure, it is possible that varying penetrance of different region specific *CDKN2A* variants or co-inheritance of other genetic modifiers could contribute to the differences. Tobacco smoke has been linked to increased penetrance of *CDKN2A* for pancreatic, upper gastrointestinal, and respiratory cancers, and it is hypothesized that it may also affect *CDKN2A* penetrance for melanoma.[4]

FAMILIAL MELANOMA MUTATIONS AND RISK OF OTHER CANCERS

Some familial cutaneous melanoma predisposition genes have also been linked to risk of other tumour types, where the incidence of specific cancers occurs within melanoma families at rates greater than expected by chance (Table 2).

Table 2 Melanoma predisposition genes and associations with other cancers

Gene	Chromosome band	Modifiers	Associated non-cutaneous melanoma cancers	Possibly associated cancers*	Refs
CDKN2A	9p21	MC1R, UVR, possibly tobacco smoke	Pancreas	ENT (tongue, oral cavity, pharynx, larynx), upper digestive (oesophagus, stomach), brain, breast, cervix, gall bladder, thyroid, leukaemia, liver, lung, lymphoma, renal	5, 6, 85, 86
CDK4	12q14	-	-	Breast, cervix, colorectal, lung, lymphoma, pancreas, stomach, uterine	17-20
BAP1	3p21.1	-	RCC, uveal melanoma, mesothelioma, BCC, cholangiocarcinoma	Bone, bladder, breast, colorectal, lung adenocarcinoma, meningioma, neuroendocrine, ovarian, paraganglioma, stomach, thyroid	21-36
MITF	3p14.2	Possibly MC1R	RCC, pancreas	Bladder, brain (glioblastoma), breast, colorectal, endometrial, leukaemia, lung, lymphoma, myeloma, prostate, stomach	55, 56, 58
TERT	5p15.33	-	-	Bladder, breast, endometrial, lung, ovarian, renal	43, 44
POT1	7q31.33	-	Glioma	Brain, breast, CLL, endometrial, leukaemia, thyroid, SCLC	39, 40, 90, 91
ACD	16q22.1	-	-	Breast, colorectal, leukaemia, lung, lymphoma	42
TERF2IP	16q23.1	-	-	Breast, cervix, meningioma, ovarian	42

BCC: basal cell carcinoma; CLL: chronic lymphocytic leukaemia; RCC: renal cell carcinoma; SCLC: small cell lung cancer; UVR: ultraviolet radiation

* Possibly associated cancers include those documented in pedigrees of affected individuals and their non-wild type untested family members

The most extensively documented association is between *CDKN2A* and pancreatic cancer, although associations have been noted for a range of other cancers.[4, 5, 84, 85] A study of carriers of the Swedish p.Arg112dup *CDKN2A* founder mutation found significantly increased risk of pancreatic cancer, upper digestive (oral cavity, tongue, pharynx, larynx, oesophagus, stomach, liver, gall bladder) cancers, and respiratory (bronchi and lung) cancers.[4] , At age 80 years, 53% of carriers were reported to have at least one of these specific cancers.[4] Interestingly, the risk of cancer was significantly higher in individuals who had ever smoked, compared with carriers who had never-smoked.[4] Upper gastrointestinal and respiratory tissues are particularly sensitive to carcinogens, and exposure to tobacco smoke and other environmental carcinogens may increase the penetrance of *CDKN2A* in these cancers in a similar manner to UVR and melanoma. An international study reported an increased risk of all non-melanoma cancers in first degree relatives of *CDKN2A* mutation carriers.[84] For mutation carriers, the lifetime risk of any cancer other than melanoma was estimated at 59% by age 85.[84]

Further to *CDKN2A* variants and melanoma risk, the 9p21 locus has been linked to a variety of other cancers. An analysis of eight different GWAS identified several significant SNPs in this region, including some variants associated with multiple cancers.[86] Of particular note may be the *CDKN2A* intronic rs3731239 SNP, which was associated with oesophageal squamous cell cancer, gastric cancer, and breast cancer.[86] Although these results to do not directly relate to specific melanoma risk SNPs, it is interesting to consider the potential impact of this region to cancer susceptibility more generally, and as a potential site for other novel cancer predisposition variants.

An association with multiple cancers has also been indicated for *POT1*.[38, 39] Other cancer types include breast cancer, small cell lung cancer, endometrial cancer, and brain tumours, which have been observed in *POT1* mutation carriers and their untested family members. There may also be a link with chronic lymphocytic leukaemia (CLL), which has somatic mutations in *POT1* at relatively high frequency, the majority of which affect the OB folds, a finding that is in keeping with alterations detected in the recent melanoma studies.[38, 39, 87, 88] One *POT1* mutation carrier had a history of both melanoma and CLL, and it is possible that a variant exists that could affect a portion of the OB fold domain that is relevant to the development of both melanoma and CLL.[38]

Additionally, *POT1* has recently been implicated in the development of glioma.[89] Three novel protein-changing variants have been described, each found in one family with a high case density of glioma. In one family with six carriers and one obligate carrier of p.G95C, three individuals

developed glioma at young ages.[89] Of six carriers in a family with a p.E450X mutation, two were affected by glioma.[89]

Glioma has previously been tentatively associated with melanoma following the observation of more melanoma cases than expected in glioma families.[90] Although the underlying basis for susceptibility is uncertain, analysis of potential glioma susceptibility loci by GWAS has identified variants in chromosome 9p21 near *CDKN2A* and *CDKN2B*.[91, 92] The glioma candidates are not in the same linkage disequilibrium block as the *CDKN2A* melanoma gene, but it suggests the possibility that this region may account for shared predisposition to both cancers.

More cancers than expected has also been found in families carrying *ACD* and *TERF2IP* mutations, which like *POT1*, affect the shelterin complex. Although the numbers are too few to be statistically significant, additional cancers in carriers with melanoma include lung, breast, bowel, and haematological malignancies, suggesting a possible *ACD*/*TERF2IP* associated spectrum of cancers.[41]

Somatic *TERT* promoter mutations have been found in a wide range of different cancer types, and the occurrence of multiple additional cancers in individuals affected by a novel germline promoter mutation suggests that these other cancers could be due to dysregulation of TERT.[42, 43] One individual was diagnosed with endometrial cancer at age 27 and melanoma at age 30. A second affected family member developed melanoma at age 20, then subsequently had ovarian cancer, renal cell carcinoma (RCC), bladder cancer, mammary carcinoma, and bronchial carcinoma before her death at age 50.[43] It has been suggested that the nucleotide sequence change in the germline variant creates a binding motif similar to one already used by the ternary complex factor Elk1, which has been demonstrated as a transcriptional regulator in breast, cervical, and endometrial cancer.[43, 93-95] Although a tenuous link, this could help explain gender related differences as well as the presence of endometrial, ovarian, and breast cancer.

A bidirectional association has been established between melanoma and RCC for sporadic cases, and a number of familial melanoma studies have also noted an over-representation of this cancer.[96] Both RCC and pancreatic cancer have been linked to the p.E318K mutation in *MITF*, and a potential connection between melanoma and lymphoma has been noted.[54, 55, 57] Mutation p.E318K upregulates hypoxia inducible factor, which has been identified as the downstream target of other known RCC predisposition genes.[54] *BAP1* has also recently been associated with the development of RCC. In an analysis of 60 French families with BAP1-reminiscent cancer clustering, RCC-

affected individuals were identified in six out of 11 families with germline *BAP1* mutations.[26] A novel variant has been detected in one American family with multiple cases of RCC but no other cancers, suggesting that germline *BAP1* mutations may rarely predispose solely to RCC.[97]

The high density of cancer in families affected by germline *BAP1* mutations suggests that this gene is a critical regulator of oncogenesis for the tumours identified.[30] The numerous functional domains of the BAP1 protein present a range of potential sites for mutation. Therefore a number of germline variants may exist, each possibly contributing to a different collection of cancers. Further to the heterogeneity of *BAP1* mutations, it is likely that modifier genes and environmental factors also impact the cancer phenotype in *BAP1* families. A BAP1 cancer cluster comprised of *c*utaneous/*o*cular melanoma, atypical *m*elanocytic proliferations, and *o*ther internal *n*eoplasms such as mesothelioma (COMMON) has been proposed as a particular syndrome.[23] However, further studies have implicated a range of other cancers as part of a possible BAP1 spectrum. In addition to RCC, possibly associated neoplasms include lung adenocarcinoma, meningioma, paraganglioma, breast cancer, neuroendrocrine tumours, gastric cancer, and basal cell carcinoma.[22, 24, 25, 27, 28] These findings hint at the prospect of many other *BAP1* associated cancers as more families are identified.

FAMILIAL CANCER SYNDROMES AND MELANOMA RISK

A number of other rare autosomal familial cancer syndromes have been described, characterised by the occurrence of multiple cancers including melanoma. These include Li-Fraumeni syndrome, xeroderma pigmentosum, Werner syndrome, and familial breast cancer. Li-Fraumeni syndrome is linked to TP53, and germline mutations are associated with breast cancer, bone and soft tissue sarcomas, brain tumours, and adrenocortical carcinomas.[98, 99] The inclusion of melanoma in the syndrome has been controversial, however a handful of melanoma cases have been reported, including one patient with a germline *TP53* mutation who presented with multiple primary cutaneous melanomas.[100] In contrast, xeroderma pigmentosum is an autosomal recessive condition caused by mutations in one of eight nucleotide excision repair genes, and the DNA repair function they encode is crucial to the cellular response to UVR-induced DNA damage.[101] Coupled with UVR damage, this failure in DNA repair predisposes to increased sun sensitivity and skin cancers. A 2,000 and 10,000 fold increase in melanoma and non-melanoma skin cancer, respectively, has been reported, as well as an increase in neural system cancers.[101] Werner syndrome is also autosomal recessive, and loss of function mutations in the *WRN* gene lead to premature aging and multiple cancer susceptibilities, with the spectrum comprising thyroid cancer, melanoma, meningioma, sarcomas, and leukaemia.[102] Analysis of tumours other than breast cancer in carriers of *BRCA1* or

BRCA2 mutations has shown that *BRCA2* defects are associated with 2.6-fold and 99.4-fold increased risks of cutaneous and uveal melanoma respectively, but there is no increase in melanoma risk associated with *BRCA1* mutation.[103, 104]

CLINICAL IMPLICATIONS AND FUTURE PRACTICE

The identification of cancer predisposition genes by genetic testing is typically only recommended when the results influence clinical decisions and treatment can be implemented to prevent or improve clinical outcomes.[105] Genetic testing in melanoma is therefore controversial, due to the relatively low frequency of high penetrance mutations and the contribution of multiple additional factors that modulate melanoma risk. Despite this, heightened surveillance and more regular skin checks could be a useful outcome for a patient with a known susceptibility.

One of the main benefits encountered from genetic testing is that it may prompt useful discussions about melanoma risk, early detection, and prevention with multiple family members. The impact of melanoma risk discussion on the effect on future sun safety behaviours has been demonstrated in a group of family members identified for *CDKN2A* testing.[106] Two years following genetic testing, individuals sustained improvements in daily sun protection and fewer sunburns, with no diminution after a negative test result.[106] Although this study is subjective, it highlights the potential positive impact of increasing awareness and education. Counselling may therefore form an opportunistic intervention to motivate preventative behaviours and minimise UVR exposure risk.

With time, it is anticipated that the data pool of presently known variants will expand, which will be particularly important for analysis of rare variants in a wider population. For families with a high cancer burden but no carriers of previously identified predisposition genes, next-generation sequencing will be key to identifying potential novel high penetrance variants and narrow the present knowledge gap. If future studies indicate clinical utility for genetic testing, it is likely that only high penetrance predisposition genes would be prioritised for gene panels dedicated to melanoma risk evaluation. Although the epistatic effect of *MC1R* variants on *CDKN2A* penetration has been noted, it is less likely that low or medium penetrance risk genes would be used as routine screening tests due to the uncertainty of predicting the clinical outcome of disease development.[3]

Progressing from attribution of melanoma risk, future practice in familial melanoma may involve novel susceptibility genes as a basis for development of early detection strategies. The possibility of combining clinical and genetic information for prognostic estimates has been proposed, where a

novel logistic regression model of two significant SNPs, histological tumour type, and stage at diagnosis had an improved discrimination of 3-year melanoma recurrence compared to histology and stage alone.[107] A recently published study analysed 2,339 SNPs in 14 autosomal genes of the Fanconi anaemia pathway, which is involved in the crosslink repair of DNA. Four SNPs were significantly associated with reduced overall survival and melanoma-specific survival, and combination of these factors with tumour stage and Breslow thickness further refined 5-year predictive ability.[108]

Although the potential for targeted treatments directed at germline mutations seems unlikely, it may be plausible in the future, particularly for high penetrance genetic variants with both germline and sporadic manifestations.

CONCLUSION

Overall, the landscape of melanoma risk genes is becoming gradually less mysterious, with the addition of *BAP1*, *POT1*, *ACD*, *TERF2IP*, and *TERT* to the known high penetrance melanoma risk genes *CDKN2A* and *CDK4*. Ongoing studies of recently identified pigmentation genes in a wider population will be highly significant in both their independent risk and the additional risk conferred by gene-gene and gene-phenotype interactions. Novel candidate genes are promising, however there likely still remains a great many to be elucidated. The contribution of melanoma risk genes to other cancers is particularly important for families with observed cancer clustering, where novel genes may also predispose to other cancers. In the future, it is plausible that melanoma risk genes could be used for genetic counseling of melanoma as well as the other cancers they influence. The most important outcome of familial melanoma research will be in clinical application, and even without genetic testing, awareness of the hereditary component of melanoma is likely to improve health promotion and advocacy as part of holistic patient care. Future research will continue to validate known risk genes in wider populations, and will also aim to discover novel predisposition genes for the large percentage of families with a high case density but no identified presently known genes. Although routine genetic testing is currently not recommended due to the complex polygenic interplay that influences the clinical picture of melanoma, the potential for predisposition genes to be utilised as screening tools, for prognostic information, and as targets for treatment may be important in future practice.

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Chapter 3

Increased incidence of bladder cancer, lymphoid leukaemia, and myeloma in a cohort of Queensland melanoma families

INTRODUCTION

In contrast to 'sporadic' cancer, occurring in the absence of family history or known risk genotype, the clustering of multiple cancers has been observed in some families. Familial risk has been proposed as a shared feature of many cancers, particularly for those diagnosed at a younger age and with multiple affected family members.[1-4] The degree to which certain cancers aggregate in families has been difficult to define, due to the heterogeneity of possible high penetrance germline mutations, low to moderate risk polymorphisms, genetic and environmental modifiers, and individual lifestyle factors.[1, 4, 5] However, it appears that risk of some cancers is more heritable than others.[5, 6]

A positive family history is associated with increased risk of melanoma, and although familial melanoma prevalence varies by geographic region, approximately 10% of Australian melanoma cases have an affected relative.[7, 9] The cumulative risk of melanoma in first degree relatives (FDRs) of cases has been estimated at 6-7% by the age of 80 years, with this risk rising to 10% if the relative with melanoma was diagnosed before age 50.[10]

The familial melanoma susceptibility gene *CDKN2A* is associated with an increased risk of cancers other than melanoma, particularly pancreatic and digestive tract cancers.[11-14] Other high-penetrance melanoma predisposition genes have also been linked to additional non-melanoma cancers, including a cancer syndrome comprising cutaneous melanoma, uveal melanoma, and mesothelioma associated with BAP1 mutations; renal cell carcinoma with *MITF* and *BAP1*; and glioma with *POT1*.[15-25]

In some families affected by melanoma, additional 'over-represented' cancers continue to be observed. For both melanoma and other cancers, rare high penetrance loci cannot entirely explain observed familial rates, and it is likely that 'familial' cancer is influenced by the contribution of multiple low risk genes and modifiers inherited by susceptible individuals.

The combination of individual risk alleles may also be important, depending on whether the effects are additive or epistatic, and thus the number of inherited variants required for oncogenesis.

Differences in populations with strong founder effects, different patterns of low-risk polymorphism inheritance, and specific environmental exposures, may result in different clusters of melanoma-associated cancer types between geographic regions.[12]

At a population level, a unique underlying predisposition for cancer is likely conferred by the combined effects of many low risk loci and exposures, and it is possible that specific cancer types share similar combinations of polymorphisms that increase overall risk.

To investigate population level cancer risk for 'melanoma' families, the present study seeks to assess the risk of cancers other than melanoma in a cohort of families with at least two first-degree relatives affected by melanoma, not selected for specific genetic mutations.

MATERIALS AND METHODS

Study inclusion

The study cohort comprises 178 families originally ascertained between 1982 and 1990 as part of the Queensland Familial Melanoma Project (QFMP), designated as 'intermediate risk' due to confirmed cases of melanoma in two first-degree relatives.[7] Melanoma was defined as melanoma in situ or invasive melanoma. Cases of lentigo maligna and Hutchinson's melanotic freckle were excluded. Of the 415 families in the 'intermediate risk' group, these 178 families had not had further contact since a follow up study (The Queensland Study of Melanoma: environmental and genetic associations (Q-MEGA)) was completed between 2002 and 2005, when one or more individuals in each family answered a structured telephone interview relating to personal and family cancer information.[26] Melanoma cases and their FDRs were considered eligible for the current study if they had given written consent or had verified death information. First-degree relatives of all confirmed melanoma cases in each family were included, regardless of which individual was the proband.

For bilineal families, both family lines were considered, to account for possible polygenic inheritance. Individuals with confirmed melanoma who married into a 'melanoma' family were only considered if they had at least one child who had given written consent or had available death information. Individuals without a genetic link to any melanoma case were excluded (i.e. related only by marriage, adoption), as were all individuals who were not alive at any point during the study period regardless of melanoma status (for reason see below).

Study period

The study period (33 years) commenced in 1982, when it first became mandatory to notify all cancers in Queensland to the Queensland Cancer Registry (QCR), and concluded at the end of 2014.

Cancer verification

Information on cancer diagnoses were obtained and verified from the following sources: histopathology from the QCR or any other source; National Death Index (NDI); written confirmation from a doctor or medical professional; genetic clinic counselling information; and original medical records or cancer information sighted and transcribed by a research nurse. In the absence of any other confirmation, a self-reported melanoma excision scar of greater than 5 cm (as documented on a historical QFMP questionnaire) was considered acceptable. Any cancer reported by an individual or relative that was not supported by any of the above verification criteria was excluded.

Cancer type

Cancers were counted only for primary events, not for metastases, unless metastatic disease was the first cancer diagnosed. In the case of metastatic disease, events were counted for the histological subtype and not the organ with metastatic cancer. In this way, an individual with metastatic melanoma to the brain would only be counted for melanoma, not brain cancer. Different cancers of the same organ/type in a single individual were counted as separate events only if they were primary cancers and were histopathologically distinct. Cancers not reportable to the QCR, such as basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) of the skin, were excluded.

Events were only counted for invasive cancers, in line with the cancer statistics reported by the QCR, defined as all invasive cancers with International Classification of Diseases for Oncology 3 (ICD-O3) site codes C00 to C80 (excluding C44 morphology codes M805 to M811, as these code for BCC and SCC).[27]

Sixteen benign or non-invasive neoplasms (i.e. with ICD-O behaviour codes of 0, 1, or 2) with histopathology confirmation were thus excluded.

Excluded neoplasms were two monoclonal gammopathies of unknown significance in two males both affected by melanoma, one parathyroid adenoma in a male FDR, one vulva intraepithelial neoplasia (VIN) III in a female FDR, one cervical intraepithelial neoplasia (CIN) I in a female FDR, one CIN II bordering on CIN III in a female affected by melanoma, and six cases of CIN III/cervical SCC in situ (five females affected by melanoma, and one FDR).

Four WHO grade I brain neoplasms were also excluded: one fibroblastic meningioma in a female FDR, one fibroblastic meningothelial meningioma in a male affected by melanoma, one meningothelial meningioma in a female FDR, and one haemangioblastoma cerebellum in a male FDR.

Cancer risk estimates

The Cancer Council Queensland publishes annual incidence of all invasive cancers, and also publishes a standardised incidence rate per 100,000 people for males, females, and total population. Annual crude incidence rates for each age and sex stratum are calculated and then applied to a standard reference population, to allow direct comparison and averages between years.

The standard population used for calculating age-standardised incidence rates by the Cancer Council Queensland is the 2001 Australian resident population, as published by the Australian Bureau of Statistics.

Based on differences in the availability of cancer incidence rates subdivided by age and sex for the study population at different periods of time, there are thus multiple valid ways that risk estimates can be derived. Cancer incidence rates are reported in the following ways: an average of incidence rates from 2008 to 2012, reported in 5 year age groups up to 85 years and over for males and females; and cancer incidence rates for each year from 1982 to 2012, reported in 15 year age groups from 35 years to 80 years and over in males and females for some cancers, and by sex only for remaining cancers. We present here data derived using two approaches: firstly based on the population statistics for the period 2008-2012; and secondly, for the period 1982-2012.

<u>Method 1: 2008-2012</u>

The expected number of cancers was calculated from age and sex specific published cancer incidence rates for Queensland. This was calculated first for all cancers using the 2008 to 2012

average incidence rate, age standardised in 5-year age groups from 0 up to 85 years and over [28]. Incidence rates expressed as a number of events per 100,000 people were divided by 100,000 and multiplied by the number of person years under observation in each age and sex specific stratum. The resulting numbers for each stratum were added to obtain 'expected' cancer events in the cohort and sub-groups for each cancer type.

Method 2: 1982-2012

The average of the cancer incidence over this time period was calculated, as the sum total divided by 31, reflecting 31 years of data.[29] As for Method 1, average incidence rates were divided by 100,000 and then multiplied by the number of person years in each age and sex stratum of the study cohort. For cancers where age stratified data were available (all invasive cancers, melanoma – used only in context of removing this number from total invasive cancers, breast, cervical, colorectal, lung, non-Hodgkin lymphoma (NHL), and prostate cancer), published cancer incidence rates per 100,000 persons for age groupings of age 35-49, age 50-64, age 65-79, and age 80 and over were used. No incidence rates were reported for the ages of 0 to 34. Therefore, to account for cancer events in persons aged 34 and younger, expected cancers for 0 to 34-year-olds were calculated by 5-year age groups from the published 2008-2012 incidence rates, and added to the total of expected cancers for age 35 to 80 years and over from 1982-2012 incidence rates.

For cancers where incidence rate data from 1982 to 2012 per 100,000 persons was only available for sex, and not stratified by age (bladder, brain, head and neck, gynaecological – combined group, ovarian, uterine, kidney, leukaemia - combined group, lymphoid leukaemia, myeloid leukaemia, lymphoma – combined Hodgkin lymphoma and NHL, myeloma, liver, mesothelioma, pancreatic, stomach, and thyroid cancer), cancer risk estimates were obtained by multiplying the average total incidence for males and females by the number of person years under observation.

Statistical analysis

The standardised incidence ratio (SIR) was computed as the ratio of observed and expected cases of cancer. As above, expected cancers were based on age and sex specific incidence rates multiplied by the number of person years in each age and sex specific stratum. A person year was defined as any part of a year under observation while the person was alive, with a maximum of 33 years from 1982 to 2014 inclusive. 95% confidence intervals were computed to test the statistical significance

of the SIRs, based on the Poisson distribution model. The difference between observed and expected cases was considered statistically significant if the 95% confidence interval did not include the value of 1.

Expected versus observed cancers and 95% confidence intervals were calculated by sex and by sub-group for individuals affected by melanoma and FDRs.

Age and sex standardized 'expected' events of melanoma were calculated for the purpose of subtracting these from the total number of expected invasive cancers, to obtain the expected number of invasive non-melanoma cancers. Melanoma risk was not analysed, as families were selected based on 'intermediate risk' melanoma status.

RESULTS

A total of 943 individuals from 178 families were included, comprising 25,264 person years of observation. There were 414 individuals affected by melanoma, 192 males and 222 females, with 5,244 and 6,722 person years of observation, respectively. There were 529 FDRs of these individuals, 250 males and 279 females, contributing 5873 and 7425 person years, respectively.

Of the 178 families, 125 (70%) had at least one individual diagnosed with non-melanoma cancer during the study period.

Of 414 individuals affected by melanoma, there were 128 non-melanoma cancer events in 102 (25%) individuals. Of the FDRs, 134 (25%) were also diagnosed with at least one non-melanoma cancer, with a total of 150 non-melanoma cancer events in this group.

The observed versus expected cancers were analysed in two different ways, as outlined in the methods.

<u>2008 to 2012 incidence rates</u>

Using the 2008 to 2012 incidence rates, in the overall cohort there was not a statistically significantly different number of total cancers observed than expected (observed, 278; expected, 291.43; SIR, 0.95; 95% CI 0.85-1.07). Bladder, haematological, and thyroid malignancies were modestly increased (Table 3).

When separated by sex, no cancers reached statistical significance in males (Table 4). In females, increases in observed numbers of bladder cancer (observed, 7; expected, 1.99; SIR, 3.52; 95% CI, 1.41-7.25) and lymphoid leukaemia (observed, 6; expected, 1.75; SIR, 3.43; 95% CI, 1.26-7.46) were statistically significant (Table 5; Figure 6).

Considering the individuals with melanoma separately, myeloma was statistically significant for the overall group (observed, 6; expected, 1.97; SIR, 3.04; 95% CI 1.12-6.62). However, when separated by sex, myeloma was only significant for females (observed, 4; expected, 0.82; SIR, 4.89; 95% CI 1.33- 12.52). Bladder cancer was also statistically significant for females affected by melanoma (observed, 4; expected, 0.87; SIR, 4.59; 95% CI, 1.25-11.76). There were slightly more renal, haematological, and thyroid cancers than expected in melanoma cases, but these cancers did not reach statistical significance.

In FDRs of individuals with melanoma, either as a combined group or stratified by sex, no cancers reached statistical significance.

1982 to 2012 incidence rates

Comparing the study population to the average age and sex standardised incidence rates from 1982 to 2012, observed versus expected total non-melanoma invasive cancers was not significantly increased (observed, 278; expected, 267.30; SIR 1.04; 95% CI 0.92-1.17).

For cancers with available age and sex standardised incidence rates, there were modest increases in observed events of NHL (16 observed, 9.71 expected) and female breast cancer (40 observed, 31.79 expected), however these differences were not statistically significant.

The remainder of cancers had incidence rates for males and females (available as an incidence rate by sex only) from 1982 to 2012. A number of cancers reached statistical significance for males and females combined – bladder, kidney, leukaemia, lymphoid leukaemia, lymphoma, myeloma, mesothelioma, pancreas, and thyroid (Table 3).

Statistically significant cancers with more than ten observed events each were bladder cancer (observed, 12; expected 3.93; SIR, 3.05; 95% CI, 1.58-5.33), leukaemia, mostly comprised of

lymphoid leukaemia (observed, 12; expected 3.73; SIR, 3.22; 95% CI, 1.66-5.63), and lymphoma (observed, 17; expected 4.63; SIR, 3.68; 95% CI, 2.14-5.88).

The only cancers with at least five events to be statistically significant in males only were lymphoma, with 9 observed and 2.38 expected cases (SIR, 3.78, 95% CI 1.73-7.18), and kidney cancer, with 7 observed and 1.85 expected cases (SIR, 3.78; 95% CI 1.52-7.79) (Table 4; Figure 7).

In females, bladder cancer (observed, 7; expected, 0.98; SIR 7.12; 95% CI 2.86-14.66), thyroid cancer (observed, 5; expected, 1.30; SIR, 3.85; 95% CI, 1.25-8.99), and haematological malignancies were statistically significant. Leukaemia (observed, 7; expected, 1.59; SIR, 4.40; 95% CI, 1.77-9.07), including lymphoid leukaemia (observed, 6; expected, 0.77; SIR, 7.81; 95% CI, 2.87-17.00), lymphoma (observed, 8; expected, 2.21; SIR, 3.62; 95% CI, 1.56-7.14), and myeloma (observed, 4; expected, 0.62; SIR, 6.43; 95% CI, 1.75-16.47) were also all statistically significant (Table 5; Figure 7).

Lymphoid leukaemia was significant both for females affected by melanoma and female FDRs. Lymphoma and myeloma remained statistically significant when considering females affected by melanoma separately, but were not significant for FDRs.

Brain cancer was increased for females in the group (observed, 4; expected, 0.82; SIR 4.87; 95% CI 1.33-12.46), mostly owing to female FDRs.

Table 3: Observed versus expected invasive cancers, combined male and female

		1982-2012* †			2008-2012		
Cancer site/type	*Observed*	*Expected*	*SIR*	*95% CI*	*Expected*	*SIR*	*95% CI*
All invasive non-melanoma	278	267.30	1.04	0.92-1.17	291.43	0.95	0.85-1.07
Bladder	12	**3.93**	**3.05**	**1.58-5.33**	7.71	1.56	0.80-2.72
Brain	5	1.76	2.84	0.92-6.64	3.50	1.43	0.46-3.33
Breast	40	31.79	1.26	0.90-1.71	36.70	1.09	0.78-1.48
Colorectal	34	42.92	0.79	0.55-1.11	43.34	0.78	0.54-1.10
Gynaecological	8	6.17	1.30	0.56-2.56	12.66	0.63	0.66-1.95
Cervical	2	2.54	0.79	0.10-2.85	1.58	1.27	2.19-9.98
Ovarian	2	1.73	1.16	0.14-4.18	3.51	0.57	0.07-2.06
Uterine	3	2.17	1.38	0.28-4.04	5.90	0.51	0.10-1.49
Leukaemia (all)	12	**3.73**	**3.22**	**1.66-5.63**	9.25	1.30	0.67-2.27
Lymphoid leukaemia	8	**1.80**	**4.44**	**1.92-8.75**	4.37	1.83	0.79-3.61
Myeloid leukaemia	4	1.53	2.62	0.71-6.70	3.24	1.23	0.19-2.71
Lymphoma (all)	17	**4.63**	**3.68**	**2.14-5.88**	12.57	1.35	0.79-2.17
NHL	16	9.71	1.65	0.94-2.68	11.84	1.35	0.77-2.19
Myeloma	6	**1.39**	**4.32**	**1.59-9.40**	4.20	1.43	0.52-3.11
Head and neck	6	3.90	1.54	0.56-3.35	8.76	0.68	0.25-1.49
Kidney	9	**3.25**	**2.77**	**1.27-5.26**	9.38	0.96	0.44-1.82
Liver	2	0.89	2.26	0.27-8.15	3.51	0.57	0.07-2.06
Lung	27	31.45	0.86	0.57-1.25	32.35	0.83	0.55-1.21
Mesothelioma	3	**0.53**	**5.71**	**1.18-16.68**	2.35	1.28	0.26-3.73
Pancreatic	7	**2.50**	**2.80**	**1.13-5.78**	7.51	0.93	0.37-1.92
Prostate	49	44.29	1.11	0.82-1.46	54.53	0.90	0.66-1.19
Stomach	4	2.68	1.49	0.41-3.82	5.16	0.78	0.21-1.98
Thyroid	7	**1.57**	**4.45**	**1.79-9.17**	4.27	1.64	0.66-3.38

Bold type indicates statistical significance.
SIR: standardised incidence ratio, calculated as observed/expected; NHL: non-Hodgkin lymphoma
* Expected cancers standardized by age and sex: all invasive cancers, breast, cervical, colorectal, lung, NHL, and prostate cancer.
† Expected cancers standardised by sex only: bladder, brain, head and neck, gynaecological – combined group, ovarian, uterine, kidney, leukaemia - combined group, lymphoid leukaemia, myeloid leukaemia, lymphoma – combined Hodgkin lymphoma and NHL, myeloma, liver, mesothelioma, pancreatic, stomach, and thyroid cancer

Table 4: Observed versus expected invasive cancers, males

		1982-2012* †			2008-2012		
Cancer site/type	*Observed*	*Expected*	*SIR*	*95% CI*	*Expected*	*SIR*	*95% CI*
All invasive non-melanoma	156	155.75	1.00	0.85-1.17	164.86	0.95	0.80-1.11
Bladder	5	2.94	1.70	0.55-3.97	5.77	0.87	0.28-2.02
Brain	1	0.91	1.10	0.03-6.13	1.88	0.53	0.01-2.96
Breast	2						
Colorectal	24	22.88	1.05	0.67-1.56	23.10	1.04	0.67-1.55
Leukaemia (all)	5	2.11	2.37	0.77-5.75	5.53	0.90	0.29-2.11
Lymphoid leukaemia	2	1.01	1.98	0.24-7.14	2.59	0.77	0.09-2.79
Myeloid leukaemia	3	0.84	3.55	0.73-10.39	1.85	1.62	0.33-4.74
Lymphoma (all)	9	**2.38**	**3.78**	**1.73-7.18**	6.94	1.30	0.59-2.46
NHL	8	5.15	1.55	0.67-3.06	6.58	1.22	0.52-2.40
Myeloma	2	0.77	2.59	0.31-9.37	2.40	0.83	0.10-3.01
Head and neck	4	2.70	1.48	0.40-3.80	6.19	0.65	0.18-1.65
Kidney	7	**1.85**	**3.78**	**1.52-7.79**	5.56	1.26	0.51-2.59
Liver	1	0.59	1.69	0.04-9.39	2.40	0.42	0.01-2.32
Lung	19	22.63	0.84	0.51-1.31	19.85	0.96	0.58-1.49
Mesothelioma	3	**0.49**	**6.18**	**1.27-18.06**	1.93	1.55	0.32-4.54
Pancreatic	4	1.29	3.11	0.85-7.97	3.73	1.07	0.29-2.75
Prostate	49	44.29	1.11	0.82-1.46	54.53	0.90	0.66-1.19
Stomach	3	1.74	1.72	0.36-5.04	3.34	0.90	0.19-2.62
Thyroid	2	0.37	5.46	0.66-19.71	1.16	1.72	0.21-6.23

Bold type indicates statistical significance.
SIR: standardised incidence ratio, calculated as observed/expected; NHL: non-Hodgkin lymphoma
* Expected cancers standardized by age and sex: all invasive cancers, breast, cervical, colorectal, lung, NHL, and prostate cancer.
† Expected cancers standardised by sex only: bladder, brain, head and neck, kidney, leukaemia - combined group, lymphoid leukaemia, myeloid leukaemia, lymphoma – combined Hodgkin lymphoma and NHL, myeloma, liver, mesothelioma, pancreatic, stomach, and thyroid cancer

Table 5: Observed versus expected invasive cancers, females

		1982-2012* †			2008-2012		
Cancer site/type	*Observed*	*Expected*	*SIR*	*95% CI*	*Expected*	*SIR*	*95% CI*
All invasive non-melanoma	122	115.24	1.06	0.88-1.26	126.14	0.97	0.80-1.15
Bladder	7	**0.98**	**7.12**	**2.86-14.67**	**1.99**	**3.52**	**1.41-7.25**
Brain	4	**0.82**	**4.87**	**1.33-12.46**	1.60	2.50	0.68-6.40
Breast	40	31.79	1.26	0.90-1.71	36.70	1.09	0.78-1.48
Colorectal	10	20.03	0.50	0.24-0.92	20.03	0.50	0.24-0.92
Gynaecological	8	6.17	1.30	0.56-2.56	12.66	0.63	0.27-1.25
Cervical	2	0.98	2.03	0.25-7.34	1.58	1.27	0.15-4.57
Ovarian	2	1.73	1.16	0.14-4.18	3.51	0.57	0.07-2.06
Uterine	3	2.17	1.38	0.28-4.04	5.90	0.51	0.10-1.49
Leukaemia (all)	7	**1.59**	**4.41**	**1.77-9.08**	3.69	1.90	0.76-3.91
Lymphoid leukaemia	6	**0.77**	**7.81**	**2.87-17.00**	**1.75**	**3.43**	**1.26-7.46**
Myeloid leukaemia	1	0.69	1.45	0.04-8.09	1.39	0.72	0.02-4.01
Lymphoma (all)	8	**2.21**	**3.62**	**1.56-7.14**	5.56	1.44	0.62-2.84
NHL	8	4.57	1.75	0.76-3.45	5.21	1.54	0.66-3.03
Myeloma	4	**0.62**	**6.43**	**1.75-16.47**	1.81	2.21	0.60-5.66
Head and neck	2	1.02	1.95	0.24-7.06	2.33	0.86	0.10-3.10
Kidney	2	1.34	1.49	0.18-5.39	3.72	0.54	0.07-1.94
Liver	1	0.27	3.70	0.09-20.63	1.04	0.96	0.02-5.36
Lung	8	9.23	0.87	0.37-1.71	12.55	0.64	0.28-1.26
Mesothelioma	0	0.89	-	-	0.43	-	-
Pancreatic	3	1.19	2.53	0.52-7.40	3.73	0.80	0.17-2.35
Prostate							
Stomach	1	0.92	1.09	0.03-6.07	1.78	0.56	0.01-3.13
Thyroid	5	**1.30**	**3.85**	**1.25-8.99**	3.32	1.51	0.49-3.51

Bold type indicates statistical significance.
SIR: standardised incidence ratio, calculated as observed/expected; NHL: non-Hodgkin lymphoma
* Expected cancers standardized by age and sex: all invasive cancers, breast, cervical, colorectal, lung, and NHL.
† Expected cancers standardised by sex only: bladder, brain, head and neck, gynaecological – combined group, ovarian, uterine, kidney, leukaemia - combined group, lymphoid leukaemia, myeloid leukaemia, lymphoma – combined Hodgkin lymphoma and NHL, myeloma, liver, mesothelioma, pancreatic, stomach, and thyroid cancer

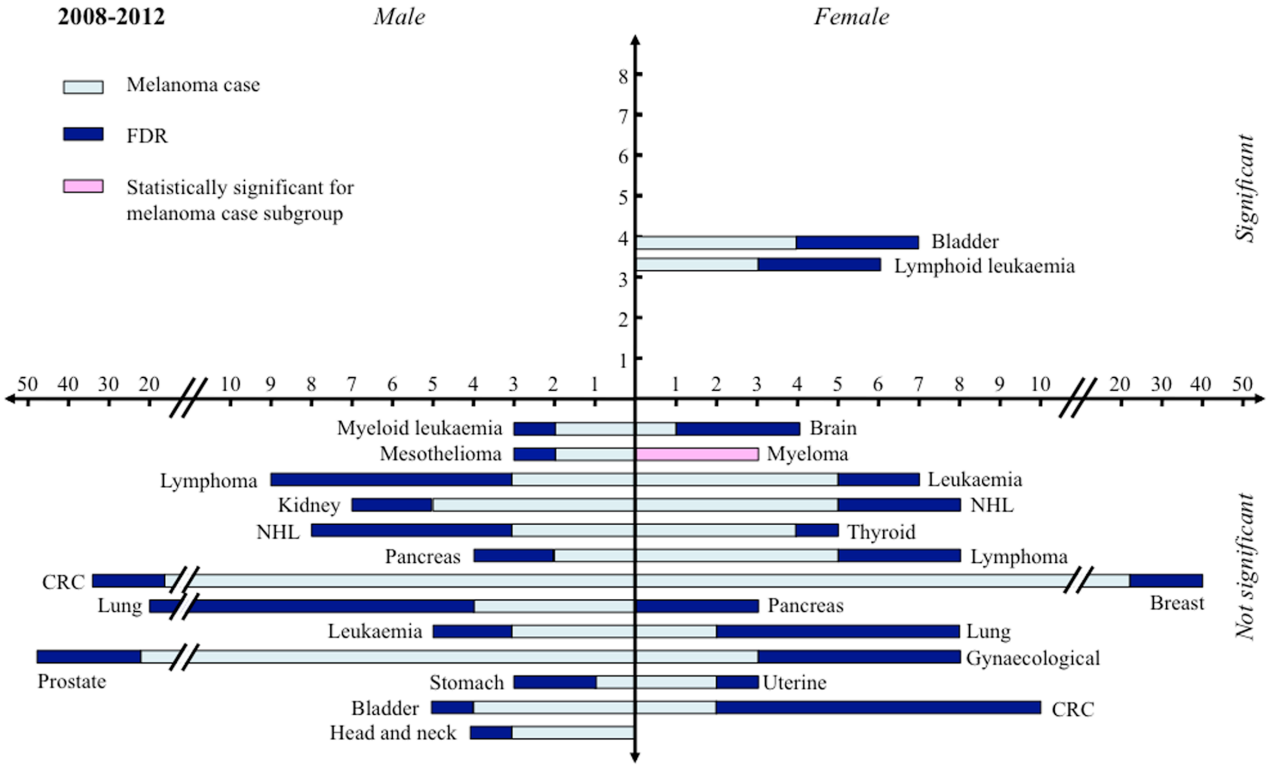

Figure 6. Frequency of cancers with ≥3 observed events, for males and females, ranked in order of significance from 2008-2012 analysis. The position of statistically significant cancers corresponds to the odds ratios for each cancer type, indicated by numbered values on the positive y axis. Cancers that were not statistically significant are ranked in order of decreasing odds ratios on the negative y axis. The values on the x axis indicate frequency of cancer. CRC: colorectal cancer; NHL: non-Hodgkin lymphoma.

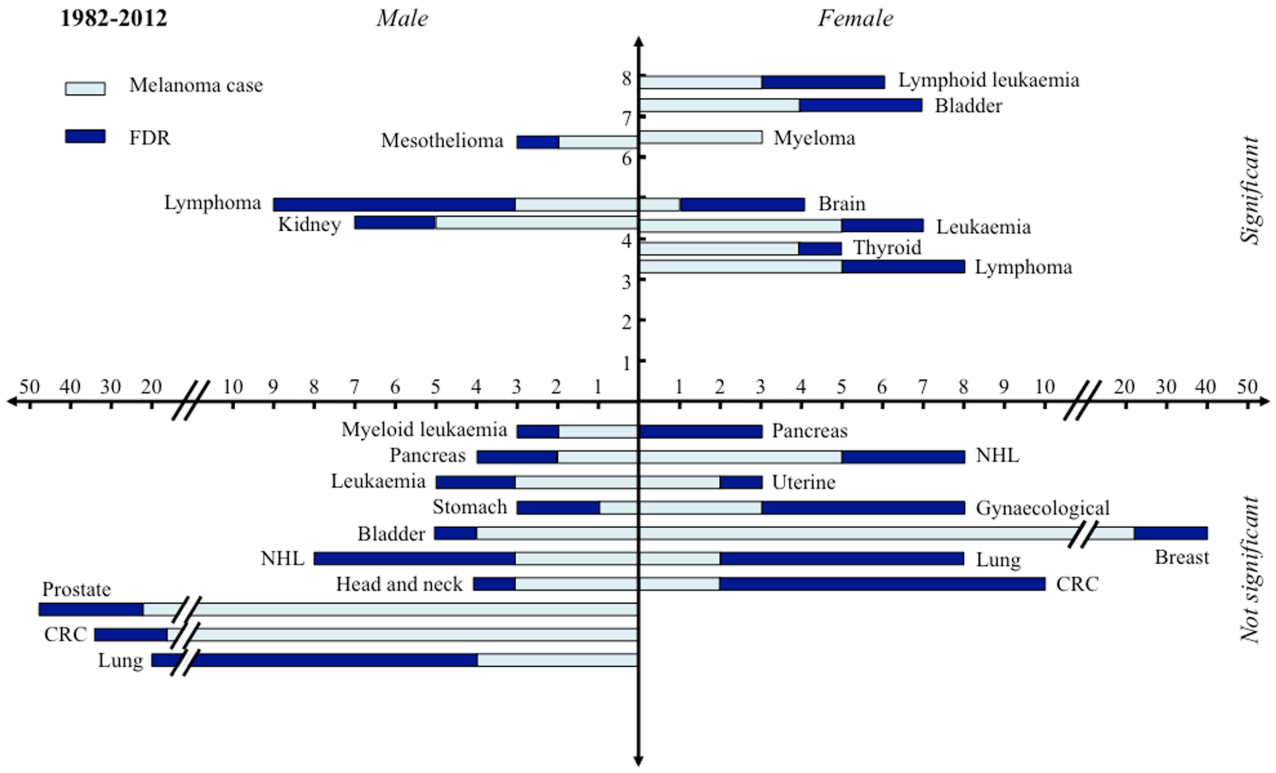

Figure 7. Frequency of cancers with ≥3 observed events, for males and females, ranked in order of significance from 1982-2012 analysis. The position of statistically significant cancers corresponds to the odds ratios for each cancer type, indicated by numbered values on the positive y axis. Cancers that were not statistically significant are ranked in order of decreasing odds ratios on the negative y axis. The values on the x axis indicate frequency of cancer. CRC: colorectal cancer; NHL: non-Hodgkin lymphoma. Expected cancers standardized by age and sex: all invasive cancers, breast, cervical, colorectal, lung, NHL, and prostate cancer. Expected cancers standardised by sex only: bladder, brain, head and neck, gynaecological – combined group, ovarian, uterine, kidney, leukaemia - combined group, lymphoid leukaemia, myeloid leukaemia, lymphoma – combined Hodgkin lymphoma and NHL, myeloma, liver, mesothelioma, pancreatic, stomach, and thyroid cancer.

DISCUSSION

This study investigated cancer in 178 'intermediate risk' melanoma families, not selected for genetic mutations. The main finding of this present analysis is the significance of bladder cancer and lymphoid leukaemia in females of the cohort, and myeloma in females affected by melanoma.

A greater number of other cancers were significant in the 1982-2012 analysis. However, the non-age standardised results must be interpreted with caution due to differences in the age distribution of the 2001 standard population and the study cohort population. While the 2008-2012 data is more precise due to narrower bands of age standardisation, the 1982-2012 method may reveal differences in cancer incidence and population trends over time that is more representative of the study population. Incidence counts of invasive cancer in Queensland have increased since 1982, and remain elevated even when standardised against a reference population to account for the changing demographics of an 'aging' population with more cancer events in older Australians.[29] Incidence rates of different cancers have also varied over the study period, possibly reflecting environmental and screening factors.[30] It is likely that the 'real' value falls somewhere between the estimates from the two methods.

Significant cancers

Bladder

Reports of a possible association between risks of bladder cancer and melanoma are varied, although one population-based study found it to be the only significant non-melanoma cancer in relatives of individuals with multiple primary melanomas.[1, 31] Cases of bladder cancer have been documented in melanoma families affected by mutations in *MITF*, *TERT*, and *BAP1*, but a heritable link between these cancer types has not been proven.[20, 25, 32] Telomerase reverse transcriptase (*TERT*) gene promoter mutations initially described in melanoma have since been identified in bladder cancer, including a rare segregating variant initially found in a large melanoma family.[32] This T>G variant, located -59 base pairs from the ATG translation start site of *TERT*, generated binding motifs for Ets and ternary complex transcription factors, and has since been noted in a bladder tumour.[33] A recent study identified germline single nucleotide substitutions in the proximal promoter of *TERT* in more than 50% of bladder tumours, including some that were also confirmed as somatic in distinct tumours.[34] The frequency (more than two-thirds) of somatic alterations in a variety of tumour stages suggests that *TERT* promoter alterations may be a common early event in

bladder tumorigenesis.[33-35] Somatic alterations in *BAP1* were also recently detected in 15% of bladder tumours.[34] Although multiple susceptibility loci have been proposed, segregating germline bladder cancer mutations are infrequently reported.[36] Several multiple-case bladder cancer families contain individuals with other cancers, but there seem no specific sites or inheritance modes.[37] In a two-case bladder cancer family, a novel germline balanced translocation affecting expression of *CDC91L1* at 20q11 was found in a 29-year-old male with bladder and renal pelvis transitional cell carcinoma.[38] In addition to a father with prostate cancer, the proband also had a brother who died at age 27 of metastatic melanoma. Given the young age of diagnosis in both brothers with bladder cancer and melanoma, it is plausible that this represents an extremely rare germline variant predisposing to both tumours. Over-expression of the cell division cycle 91-like 1 (*CDC91L1*) protein (75%) and micro-RNA (30%) in bladder cancer has subsequently been found in primary bladder carcinomas and cell lines.[39] In our study, more women than men were affected by bladder cancer, in contrast to higher population incidence in men worldwide. Tobacco smoke exposure that was historically biased toward men has now equalised, and despite the known vulnerability of bladder tissue to smoking, rates of male and female cancer have not matched modern smoking trends.[40] Causes of bladder cancer in women specifically have been inconclusive, with varying reports on parity, menopause, and hormone replacement therapy.[41]

Lymphoid leukaemia

A bidirectional association between melanoma and leukaemia has been established, and melanoma risk following CLL appears particularly increased in the Australian population.[42-45] A host of factors including environmental ultraviolet light exposure, chronic immunosuppression, and genetic components have been proposed.[42] Although lymphoid leukaemia has a strong genetic component for concordant cancer, linkage studies have failed to account for familial risk. However, a number of SNPs have demonstrated significance, and it is proposed that familial and sporadic CLL share many common elements. One novel variant allele, of *DAPK1* at chromosome band 9q22, was found to segregate with CLL in a six-case family, and was initially considered a private mutation until recent detection of germline *DAPK1* allele-specific expression in 14% of tested CLL cases.[46, 47] A link between melanoma and CLL has been identified following the discovery of a shared mutation in *POT1*, in the germline of a melanoma family and somatically in CLL.[21, 48] One P*OT1* germline mutation carrier had a history of both cancers, and it is possible that a common variant could influence cancer pathways for both melanoma and leukaemia.[21, 22, 48] Like *POT1*, the recently identified melanoma predisposition gene *ACD* is also involved in maintenance of telomere length as part of the shelterin complex, and the presence of both melanoma and leukaemia in an *ACD*

mutation carrier could feasibly represent a shared link.[49] An over-representation of females with lymphoid leukaemia in our cohort may be explained by a finding of a greater affected proportion of females with familial CLL compared to sporadic CLL. It is projected that sex specific differences in penetrance or modifiers may be a feature of the discrepancy.[50]

Myeloma

A significantly increased risk of myeloma for FDRs of melanoma cases has been noted in both the Utah and Swedish population databases, although the reverse has not been detected in familial multiple myeloma.[1, 2, 51, 52] Studies on familial clustering of myeloma have demonstrated increased risk of concordant cancer, as well as leukaemia (particularly CLL), and a common aetiologic pattern for the clustering of these cancers has been proposed.[51, 52] Other cancers linked to familial myeloma include colorectal, breast, non-thyroid endocrine, and prostate cancer.[52] A higher risk of myeloma has been identified for daughters of affected cases, with the highest risk in daughters of affected mothers (SIR 4.58).[51] This sex correlation replicates previous results, and a female predilection possibly represents a heritable sex-specific modifier or common susceptibility, which may explain the findings of significance for females only in our cohort.[51] Most family studies suggest an autosomal dominant mode of inheritance, with low penetrance for myeloma.[52] A genetic link between myeloma and melanoma has been established in one family, suggesting the high penetrance melanoma risk gene *CDKN2A* also acts as a low penetrance susceptibility gene for myeloma.[53] In this study, a germline *CDKN2A* mutation was present in four family members with melanoma and one with myeloma, and loss of heterozygosity studies on bone marrow of the individual affected by myeloma demonstrated loss of the wild-type *CDKN2A* allele in malignant plasma cells.[53] Of seven other risk loci predisposing to myeloma, two have possible links to melanoma.[54-56] A telomere link may be plausible via a SNP at 3q26.2 mapping 5' to the gene encoding the telomere RNA component (TERC) that helps maintain telomere ends in combination with *TERT*, a known high penetrance melanoma gene.[55] A common mechanism via the p16INK4a/Rb and ARF/p53 pathways may also exist, as a SNP at 22q13.1 localising to chromobox homolog 7 (*CBX7*) influences these pathways through cooperation with the oncogene *MYC*.[55] A study of temporal associations between myeloma and other neoplasms identified 5 cases of melanoma and myeloma in the same individuals, with a median time of 5 years between melanoma and myeloma being diagnosed.[57]

Additional neoplasms in the same individual are important to consider not only in the context of heritable risk factors, but also in relation to the possible contribution of the primary cancer to the

development of a subsequent cancer. Field cancerisation from treatment with radiation and chemotherapy has been associated with ensuing haematological malignancies, and also radiation-sensitive tissue like breast and thyroid.[58] However, a radiation-induced effect in our cohort seems unlikely given that surgery is the main treatment for melanoma, and the relatively long time from melanoma to diagnosis of first haematological malignancy (median 18.5 years). The development of CLL or NHL in a study of melanoma patients treated with surgery only suggests that the association is unrelated to prior treatment, consistent with reports of CLL as non-radiogenic.[59, 60] Myeloma has also not been reliably associated with radiotherapy.[61] It is likely that multiple neoplasms in the same individual are related to an underlying predisposition for cancer comprised of genetic and non-radiation environmental factors.

MULTIPLE CANCERS

Further to statistically significant cancers, the presence of multiple cancers in some families and individuals is of interest. Fifteen individuals had three different types of cancer – at least one melanoma, and at least two other types of invasive cancer (Table 6).

Table 6 Individuals affected by melanoma and at least two other invasive cancers, in order of diagnosis

First cancer	Second cancer	Third cancer	Fourth cancer	Fifth cancer
Females				
Melanoma	CLL	NHL	-	-
Melanoma x 4	Endometrial	Thyroid	-	-
Melanoma	Breast	Myeloma	-	-
Melanoma	Breast	CRC	-	-
Melanoma	NHL	CLL	-	-
Melanoma	Myeloma	CML	-	-
Males				
Thyroid	Melanoma	RCC	-	-
RCC	Prostate	Melanoma	-	-
Prostate	Breast	Parotid	Melanoma	-
Melanoma	Prostate	Mesothelioma	-	-
Melanoma	NHL	RCC	CRC	Prostate
Melanoma x 2	Hodgkin Lymphoma	CML	-	-
Melanoma	Prostate	NHL	CLL	-
Melanoma x4	CRC	Gallbladder	-	-
Melanoma	CRC	AML	-	-

AML: acute myeloid leukaemia; CLL: chronic lymphocytic leukaemia; CML: chronic myeloid leukaemia; CRC: colorectal cancer; NHL: non-Hodgkin lymphoma; RCC: renal cell carcinoma

Relatively uncommon cancers that were observed in these individuals include renal cell carcinoma, mesothelioma, and cholangiocarcinoma (interestingly, all cancers that are associated with *BAP1* germline mutations), and thyroid cancer. Eight of 15 individuals had a haematological malignancy, including six leukaemias (three lymphoid leukaemia, and three myeloid leukaemia).

In sixteen melanoma-dense families, with four or more individuals affected by melanoma, 15 families had at least one individual affected by another type of invasive cancer. These cancers included bladder, breast, glioma, lymphoid leukaemia, lymphoma, mesothelioma, and kidney cancer. Although few in number, the presence of bladder cancer, lymphoid leukaemia, and myeloma in melanoma-dense families supports the possibility of common risk polymorphisms shared by these cancer types. Common polymorphisms predisposing to cancer in general are also supported by the presence of more common cancers in these families, in contrast to the cohort findings. Of the 16 families, eight had at least one case of prostate cancer, six had colorectal cancer, six had lung cancer, and five had breast cancer. Of three mesothelioma events in the cohort, two were in cancer-dense families (a five-case family, and a six-case family). Although the numbers are too few to be statistically relevant at a population level, the cancer density (and types) of these families warrants further investigation for potential germline mutations, particularly in *BAP1*.

Compared with cancer associations for known high penetrance melanoma genes, the seven observed pancreatic cancers were not significant by age standardised analysis, which contrasts with the frequency of pancreatic cancer in *CDKN2A* mutation-positive families. As *CDKN2A* is the most common high penetrance mutation, it seems that more pancreatic cancer would be expected, however this finding may be consistent with Australian data that demonstrates fewer cases of pancreatic cancer in *CDKN2A* families than international counterparts.[1, 11, 12, 62] It also echoes the findings in the Utah population, where pancreatic cancer was not increased. Suggested contributing factors are the relatively low number of families affected by *CDKN2A* mutations, and the heterogeneity of pancreatic cancer predisposition in families that do carry *CDKN2A* mutations.[1, 5]

Further to pancreatic cancer, the present study has not demonstrated associations for all significant cancer types found in population studies of melanoma families. It is possible that the sample size has been too small to detect an association, but also that a difference in the low risk genetic polymorphisms and environmental exposures of the Queensland study population predisposes to specific cancer types. Although this study reflects population level cancer risk, it is also possible that some cancers may be attributed to a small number of families with undetected mutations in high-penetrance melanoma predisposition genes.

CONCLUSION

This pilot hypothesis-generating study demonstrates a possible link between melanoma and other cancers in individuals affected by melanoma and their FDRs, particularly bladder cancer and lymphoid leukaemia in females, and multiple myeloma in females affected by melanoma. Associations we have found here for the above over-represented cancers require replication and validation in an independent data set.

An over-representation of other cancers in melanoma families hints at the possibility of common pathways for oncogenesis, including a likely multi-hit model of many low risk heritable polymorphisms and other modifiers that underpin susceptibility to invasive malignancies.

It is possible to conduct genetic testing for known high penetrance germline mutations predisposing to melanoma, however the low yield at a population level and likely polygenic risk modification raises questions about clinical utility. Although estimating a polygenic risk score has been proposed, incomplete penetrance and multiple environmental modifiers and other lifetime exposure risks create difficulty in translating plausible associations to clinical benefit. The main implication for clinical application of familial cancer association research at the population level is likely in the field of primary health care, in providing appropriate counselling and information regarding cancer risk and prevention strategies for cancers linked to familial melanoma.

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Chapter 4

Investigation of the mutational landscape in high case density melanoma families and individuals with three or more invasive cancer types

INTRODUCTION

For families in the cohort described in Chapter 3 with a high case density of melanoma, the presence of heritable germline variants may be an important component of cancer susceptibility. Melanoma predisposition for some families is linked to mutations in known high penetrance melanoma risk genes, as discussed in Chapter 2. However, the number of families that do not carry a known high penetrance mutation infers that even in those with a relatively high melanoma case density, it is likely that multiple novel and rare germline mutations of low to moderate penetrance collectively raise overall familial cancer susceptibility. Further to melanoma, the contribution of 'melanoma' risk genes to other cancer types is increasingly evident. For individuals with multiple cancer types including melanoma, it is plausible that mutations affecting common pathways in oncogenesis predispose to a variety of tumour types. To assess the possible contribution of germline mutations to melanoma predisposition and also other cancers, we used whole exome sequencing (WES) to analyse DNA from individuals in eight families with a high melanoma case density, and eleven individuals with three or more types of invasive cancer.

MATERIALS AND METHODS

Study inclusion

The study cohort of 178 families was ascertained from the QFMP, as discussed in Chapter 2. Families were selected for WES on the basis of high melanoma case density, defined as four or more family members with melanoma, and then further prioritized on the basis of family bloodline, relatively young age of onset, multiple primary melanomas, presence of other cancers previously associated with melanoma, and availability of DNA samples for melanoma cases. Families remained designated as 'intermediate risk' as per the original study, regardless of subsequent new cases of melanoma. Individuals from the 178 families were selected for WES on the basis of three or more cancer types including melanoma in a single individual. Individuals with young age of onset, multiple primary melanomas, uncommon cancer types, or more than three different cancer types were prioritised for whole genome sequencing (WGS).

DNA samples

DNA samples from whole blood were obtained with consent as part of the original QFMP project and stored at QIMR Berghofer. Only existing samples were sent for sequencing.

Whole-exome sequencing and data analysis

WES for six cases using the SureSelectXT Target Enrichment System for Illumina Version B.2, and WGS for five cases, was conducted using the HiSeq 4000 platform. Paired-end reads of 75-100 bp were generated, with mean coverage of 60-96X.

Aligning Reads (fastq → bam)

Raw sequence reads (in fastq format) were aligned to the human reference genome (hg19) using the Burrows-Wheeler Aligner.[1] Reads were adjusted to conform to standard SAM format using an in-house tool*, reads were sorted with respect to genomic coordinate using samtools, duplicate reads marked with Picard, and reads were re-aligned against known indels and base qualities were re-calibrated using the Genome Analysis Toolkit.[2, 3]

Calling SNVs and small indels (bam → vcf)

Raw variants were detected using samtools and bcftools.[4] Variant Indels were verified *in silico*† and double-nucleotide variants detected and phased using in-house tools‡. Variants were fully annotated with ANNOVAR including dbSNP as well as allele frequencies from 1000 Genomes Project and NHLBI Exome Sequencing Project.[5] ANNOVAR also provides predictions of the effect the variant might have on the encoded protein including predictions from Sorting Intolerant from Tolerant (SIFT), Polymorphism Phenotyping v2 (PolyPhen2), Gerp++, LRT, MutationTaster, and PhyloP.

Analysis of candidate genes

Variants were separated into two groups: novel and rare. Novel variants had never been observed in the dbSNP or ESP6500 databases, whereas rare exonic variants had been previously observed at a frequency of <1% in either dbSNP or ESP6500. Candidate novel and rare segregating variants were identified and prioritised by known existing roles as melanoma predisposition genes, genes known

* Mapping quality is set to zero and CIGAR is set to empty.
† Reads overlapping with indel are aligned against candidate alleles, reads that have a significant best alignment are counted, and allele counts (AD) in VCF are updated.
‡ Adjacent SNVs are identified and reads are interrogated to determine genotype, counts, and likelihoods.

to be somatically mutated in melanoma or other cancers, and genes known to predispose to other cancers. For all novel and rare segregating variants designated as 'damaging' by SIFT, 'damaging' or 'probably damaging' by PolyPhen2, or 'disease causing' by MutationTaster programs, the genes were referenced against the NCBI gene database to assess potential contribution to cancer. Variants with a total count that was higher than the number of sequenced individuals in each family were excluded, to minimise confounding by errors in sequencing or sequence tag alignment.

RESULTS

Eight families were selected for WES. Each family had four or more melanoma cases, and at least three individuals with DNA samples available. A total of 15 novel segregating exonic variants and one novel segregating splicing variant were identified in seven families.

Novel variants that segregated were identified in the genes *MAGI1*, *MAP4K4*, *MCC*, and *ROS1* in family 007178; *DGKA*, *DUSP27*, and *SOX1* in a three-case bloodline subgroup of family 010482, and *PARK7* in a four-case bloodline subgroup of the same family; *SETD5* and *TP53BP1* in family 012081; *NEK7* in family 012828; *ERCC3* in family 050904; *MACF1*, *MX2*, and *TNK2* in family 051656; and *GRIN2C* in family 052448.

Rare segregating variants in known cancer genes or possible cancer genes were found in family 007178 (*ERBB3*, *MAP3K6*, *EDNRB*); the 3 case subgroup of family 010482 (*CKAP2*, *HUS1*, *PDZD2*); the 4 case subgroup of family 010482 (*MAP3K11*); family 050904 (*ABCB5*, *MUTYH*); family 051656 (*FANCI*, *KDM1B*, *PML*, *SLK*, *WWOX*); and family 052448 (*TYRP1*). Novel and rare variants that did not segregate were identified in other families.

Fifteen individuals affected by at least three invasive cancer types including melanoma were identified in the study cohort, six females and nine males. Three individuals who had not provided a DNA sample were excluded, as was an individual whose sample could not be located. Twenty-nine genes of interest containing novel variants were identified, including several genes (*APC*, *CDH1*, *MAGI1*, *MAP3K13*, *MAP3K4*, *PLK5*, and *POLD1*) with novel variants in two or more individuals (Figure 8). Rare melanoma or possibly cancer-associated variants were found in *APC, ARID4A, ASXL2, BAP1, BARD1, BCR, BRCA2, CBLB, CDKN2A, EDNRB, ERBB3, ERCC6L2, ERCC8, FANCC, FANCF, FANCG, FANCI, MAP3K10, MAP4K3, MC1R, MLH3, OCA2, PML, POLD1, POT1, RAD51C, RET, TERT, TET2, XRCC4, XRCC5* (Figure 9).

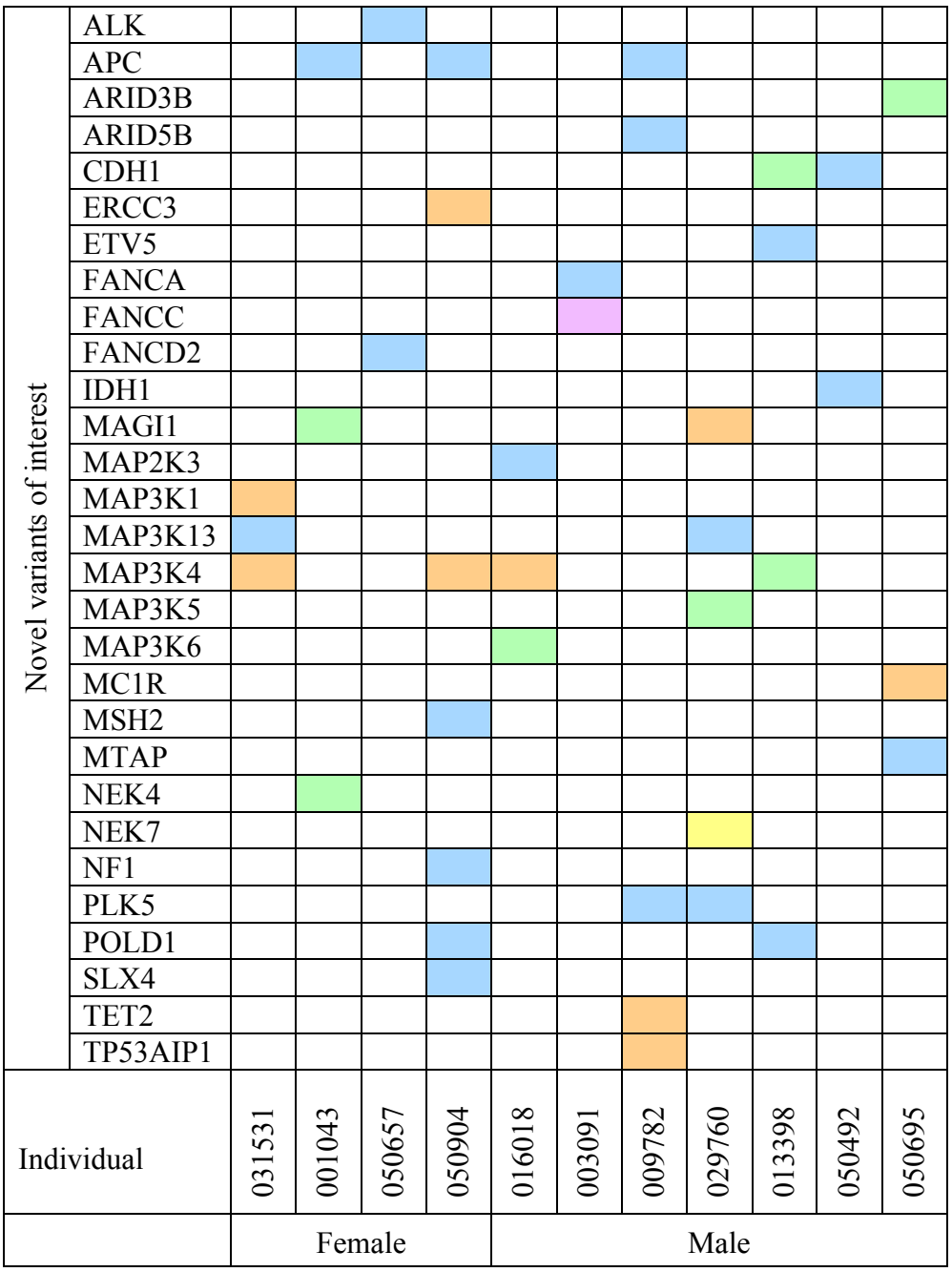

Figure 8. Novel gene variants in individuals with three or more invasive cancers

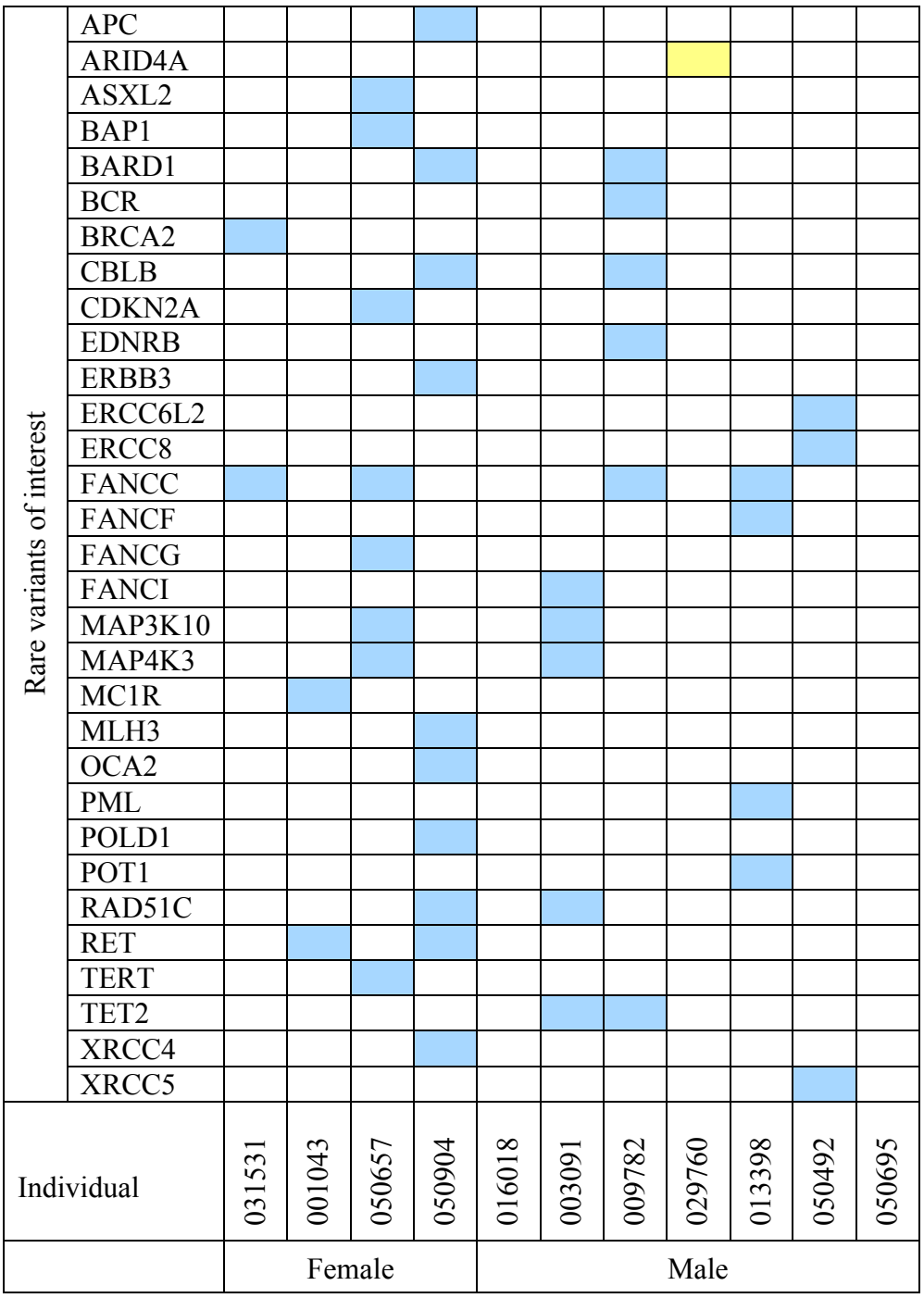

Figure 9. Rare gene variants in individuals with three or more invasive cancers

DISCUSSION

Novel and rare variants in families

007178

Four novel segregating mutations were found in this family: *MAGI1*, *MAP4K4*, *MCC*, and *ROS1* (Table 7a). Rare segregating mutations were noted in *ERBB3*, *MAP3K6*, *EDNRB*, and *MC1R*, as well as additional rare mutations in *APC*, *ARID3A*, *BRCA1*, and *BRCA2* that did not segregate in all four tested family members (Table 7b). None of the five individuals affected by melanoma had any other cancer. In other members of the family, a son of the proband developed colorectal cancer (Figure 10).

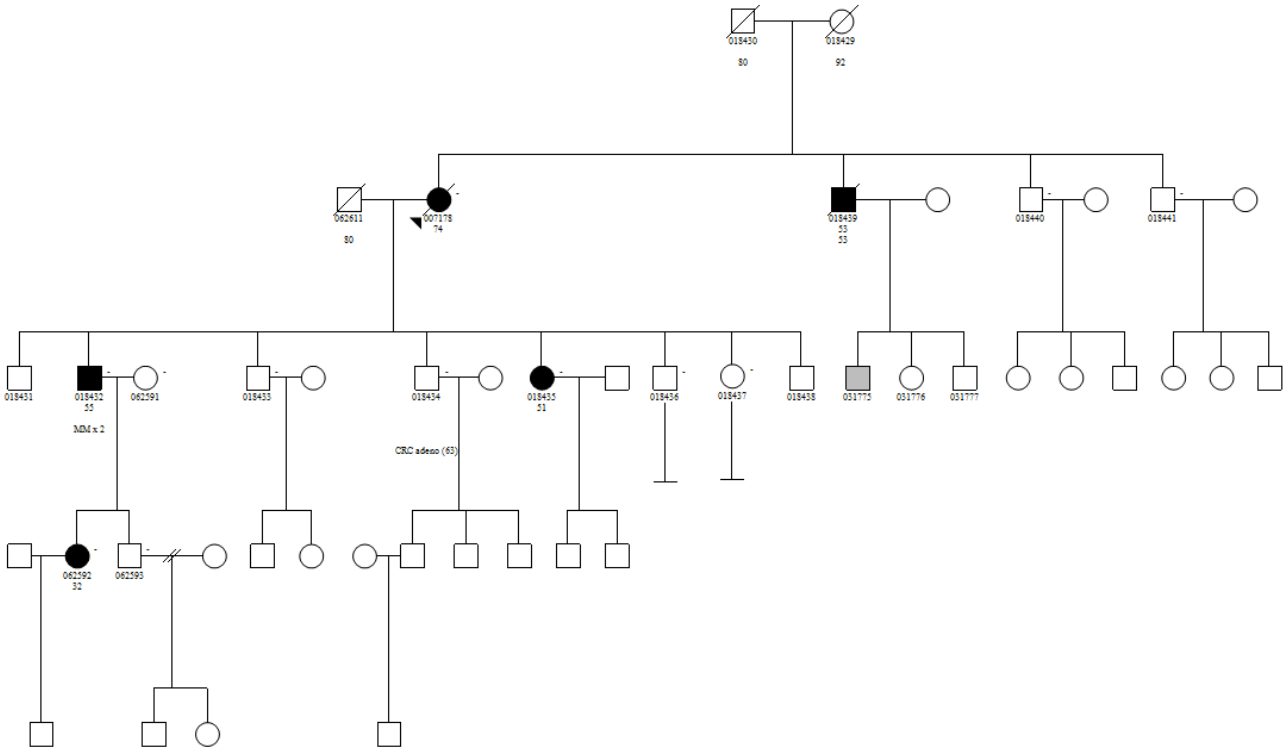

Figure 10. Pedigree of family 007178. Individuals affected by melanoma (confirmed by criteria defined in chapter 3) are shown as filled black symbols, individuals with unconfirmed melanoma are shown as filled grey symbols. Males are represented by squares, and females by circles, with deceased individuals indicated by a diagonal line. The proband is signified by a black arrow. The text under each individual symbol denotes (from top to bottom): individual ID number, age at first melanoma diagnosis, and age at death. The above pedigree legend applies to all family pedigrees in this chapter.

Table 7a: Novel variants of interest in family 007178					
	MAGI1	**MAP4K4**	**MCC**	**ROS1**	**ASXL1**
007178	nfsins	G827S	nfsins	A2106S	Q588X
018435	nfsins	G827S	nfsins	A2106S	WT
062592	nfsins	G827S	nfsins	A2106S	WT
nfsins: non-frameshift insertion					

Novel segregating variants:

MAGI1

MAGI1 codes for proteins that maintain junctional complexes via interaction with PTEN, and which play a key role in regulating cell-cell contacts.[6] A novel nonframeshift substitution, c.3138_3146insCCCAGAGCC, introduces three further amino acids, and the gene has been reported as somatically mutated in up to 25% of melanoma tissue samples. Abnormal expression of *MAGI1* in vitro influences adhesion and invasive potential of cancer cells, and the gene has also been associated with colon cancer, small intestine neuroendocrine tumours, hepatocellular carcinoma, and primary ALL.[6-9]

MAP4K4

MAP4K4 is involved in cancer cell growth, migration, and apoptosis via downstream effects on multiple targets.[10] A novel missense mutation, p.Gly827Ser, segregated in this family, and although *MAPK4K* has not specifically been associated with melanoma, the MAPK pathway has been consistently linked to melanoma and other cancers. *MAP4K4* has been implicated in many different cancer types, and overexpression is an independent predictor of poor prognosis for hepatocellular carcinoma, lung adenocarcinoma, and colorectal cancer.[11-13] It has also been identified as a biomarker of prostate cancer aggressiveness, and is associated with laryngeal and lung cancer, via regulation of the MAP4K4/JNK apoptosis pathway by SOX2.[14, 15]

MCC

MCC is proposed to act as both a tumour suppressor gene and an oncogene, through diverse actions on multiple pathways. Repression or loss of *MCC* in both liver and colorectal cancer influences the β-catenin pathway, where dysregulation leads to unchecked degradation and consequent accumulation of oncogenic β-catenin.[16] In addition to functioning as a tumour suppressor, mouse models have demonstrated that *MCC* mutations can drive oncogenesis in colorectal cancer.[17] In contrast to silenced *MCC* expression in colorectal and liver cancer, oncogenic over-expression of *MCC* has been noted in a range of B cell malignancies, including NHL and myeloma.[18] The segregating variant in this family, c.44_46insACG, adds an in-frame threonine. Although therefore less likely to be deleterious, it is possible that tumour suppressor function could be impaired.

ROS1

ROS1 is a proto-oncogene that codes for an integral membrane protein with activity as a tyrosine kinase, and influences cell proliferation, growth, and survival by likely downstream activation of several pathways including PI3K-mTOR signalling. ROS1 impacts cancer development of multiple tumour types, and its role as a driver oncogene in glioblastoma and NSCLC has made it a promising target for multi-target tyrosine kinase inhibitors.[19, 20] The involvement of *ROS1* in known melanoma pathways, and the presence of the novel segregating missense mutation p.Ala2106Ser in the tyrosine kinase domain of ROS1, hints at a likely role for this variant in predisposing to melanoma.[21]

Table 7b: Rare variants of interest in family 007178								
Gene:	**ERBB3**		**MAP3K6**		**EDNRB**		**MC1R**	
	AA change	rs number	AA change	rs number	AA change	rs number	AA change	rs number
007178	E1196G	rs147436223	splicing	rs55841735	G57S	rs1801710	R142H	rs11547464
018435	E1196G	rs147436223	splicing	rs55841735	G57S	rs1801710	R142H	rs11547464
062592	E1196G	rs147436223	splicing	rs55841735	G57S	rs1801710	WT	-
Gene:	**APC**		**ARID3A**		**BRCA1**		**BRCA2**	
	AA change	rs number	AA change	rs number	AA change	rs number	AA change	rs number
007178	R109W	rs139196838	R564Q	rs143689585	WT	-	WT	-
018435	WT	-	WT	-	R1300G	rs28897689	WT	-
062592	R109W	rs139196838	R564Q	rs143689585	WT	-	K3326X	rs11571833
AA: amino acid, rs: reference SNP								

Rare segregating variants:

ERBB3

ERBB3 encodes for ErbB3, also known as HER3, a membrane bound protein that forms active heterodimers with other ErbB receptor tyrosine kinase family members including ErbB2. The ErbB2-ErbB3 dimer allows activation of multiple downstream pathways, including the MAPK and PI3K/AKT pathways.[22] In connection with ErbB2, ErbB3 has been associated with tumour proliferation and chemoresistance, as well as disease recurrence and metastasis. The rare missense variant p.Glu1196Gly (c.3587A>G, rs147436223) affects the C-terminal binding tail of the intracellular domain of ErbB3, and is designated as damaging on both SIFT and PolyPhen2. In somatic cancer, the gene product is associated with head and neck SCC, CRC, and breast cancer.[23, 24]

MAP3K6

A splicing mutation (rs55841735) was identifed in *MAP3K6*, which encodes a serine/threonine protein kinase that interacts with MAP3K5. The interaction between the two proteins is key in regulating downstream pathways due to their opposing effects, where MAP3K6 is a tumour suppressor that promotes apoptosis, in contrast to the anti-apoptosis and pro-inflammatory effects of MAP3K5. A variety of *MAP3K6* germline variants have been identified in families with familial gastric cancer, although all variants thus far have been private mutations.[25] MAP3K6 may also be relevant in skin cancer. A mouse model found that *Map3k6* knockout mice develop significantly more skin tumours when exposed to an inflammatory stimulus, with an intermediate phenotype for heterozygous mice.[26]

EDNRB

The rare missense mutation p.Gly57Ser (rs rs1801710) affects the extracellular domain of the EDNRB protein, and was initially identified as a heterozygous variation in a Hirschsprung disease (aganglionic megacolon) proband.[27] The mutation was inherited from an unaffected carrier, suggesting incomplete penetrance, and it is possible that loss of heterozygosity and/or co-modifiers are required to express a disease phenotype.[27, 28] The mutation has also been seen at low frequency in population-based studies, and further in vivo research suggests that the G57S variant impacts the cAMP signalling pathway by reduced inhibition of adenylate cyclase.[29] While carriers of one variant copy of *EDNRB* may develop Hirschsprung disease, homozygous mutations are associated with Waardenburg syndrome type IVa.[27] Mutations in *EDNRB* alter signalling that is crucial for development and migration of melanocyte precursors from the neural crest, and the diverse phenotypic effects range from the typical white forelock and striking pale blue eye colour seen in Waardenburg syndrome, to melanoma.[27, 30] Mouse models suggest that decreased EDNRB expression transforms benign melanocytic tumour to melanoma, and EDNRB has recently been explored as a candidate for targeted therapy, with promising initial in vivo results.[31, 32] *EDNRB* polymorphisms have not been linked to sporadic melanoma at the population level, however a role has been proposed for individuals with a positive melanoma family history.[33] A family carrying mutations in both *CDK4* and in *EDNRB* has been described, and it is possible that epistatic effects influence penetrance.[34]

010482

This 5-case bilineal family can be separated into two family groups – a 3-case family comprising the father and his two children, and a 4-case family comprising the mother, her brother, and her two children. In the overall group, a number of non-segregating mutations were observed. When separated into maternal and paternal bloodlines, some of these mutations segregated in a single group. In the 3-case family group, *DGKA*, *DUSP27*, and *SOX1* variants segregated in all three individuals (Table 8a). In the 4-case family group, a *PARK7* variant segregated in all four individuals. Rare segregating mutations were found in *CKAP2* and *HUS1* in the 3-case group, and in *MAP3K11* in the 4-case group (Table 8b). Rare non-segregating mutations were found in *APC*, *AXIN1*, and *MSH6*. Additional non-melanoma cancers in this family include prostate cancer in a male affected by melanoma (Figure 11).

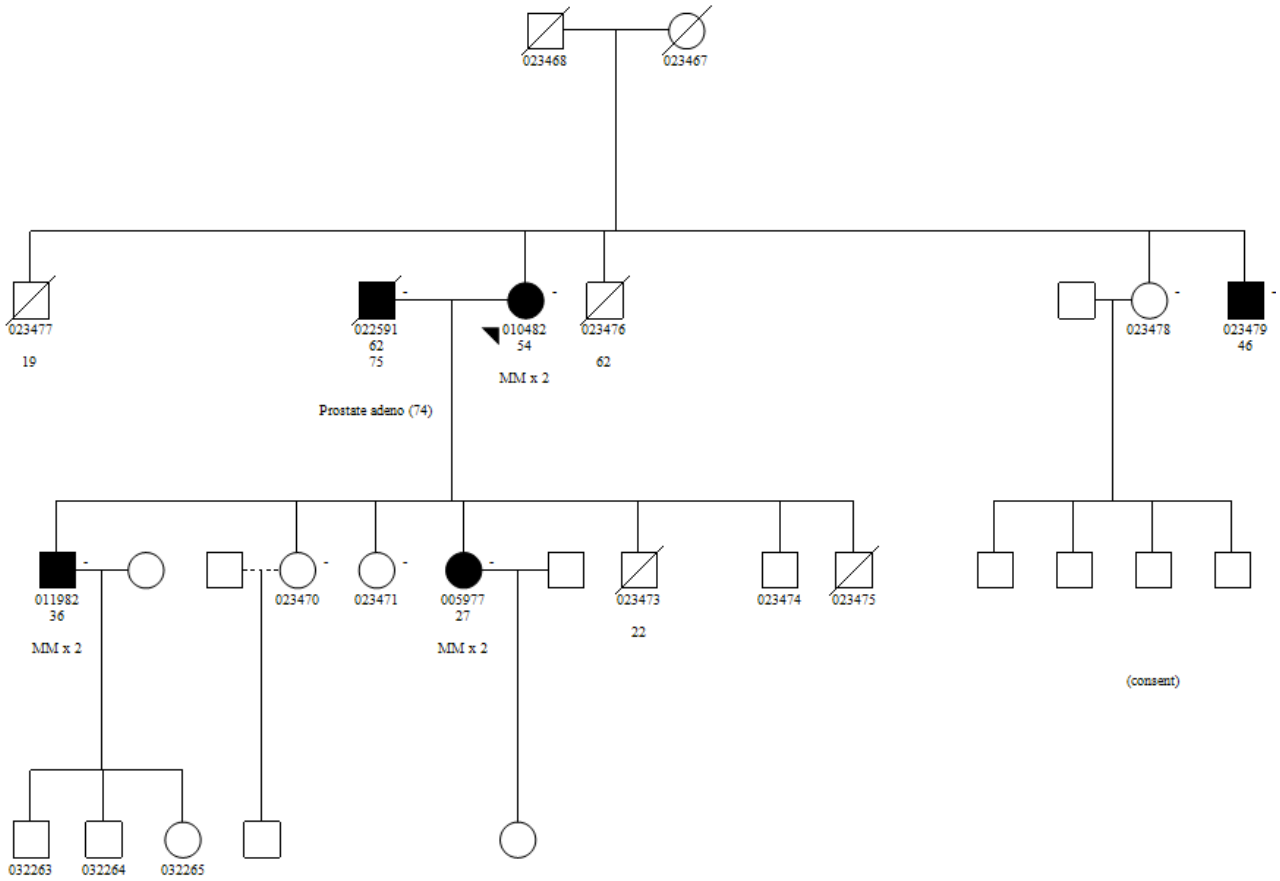

Figure 11. Pedigree of family 010482

Table 8a: Novel variants of interest in bilineal family 010482						
	Overall group					
	CHEK1	**DGKA**	**DUSP27**	**GLI2**	**PARK7**	**SOX1**
005977	WT	V379I	K738E	WT	A29G	nfsins
010482	WT	WT	WT	G624S	A29G	WT
011982	WT	V379I	K738E	G624S	A29G	nfsins
022591	F70I	V379I	K738E	WT	WT	nfsins
023479	WT	WT	WT	WT	A29G	WT
		3 case family group				4 case
		DGKA	**DUSP27**	**SOX1**		**PARK7**
005977		V379I	K738E	nfsins		A29G
010482						A29G
011982		V379I	K738E	nfsins		A29G
022591		V379I	K738E	nfsins		
023479						A29G
3 case: two affected children and their father; 4 case: two affected children, their mother, and their maternal uncle. nfsins: non-frameshift insertion						

Novel segregating variants:

DGKA

The novel missense substitution p.Val379Ile (c.1135G>A; NM_001345) in the diacylglycerol kinase alpha (DGKα) catalytic domain resultsin a damaging variant that has previously been observed as a somatic mutation.[21] DGKα phosphorylates diacylglycerol to generate phosphatidic acid, thereby regulating the concentration of these two lipid second messengers and their downstream effects.[35] Proposed effects include cell migration and invasion in a variety of tumour types, including breast cancer, glioblastoma, pancreatic cancer, hepatocellular carcinoma, lymphoma, and melanoma.[36-41] One proposed effect of DGKα in melanoma cells is the specific suppression of TNFα-induced apoptosis by catalytic action.[41] Given that the V379I mutation impacts the catalytic domain, it is plausible that damaging effects may arise due to dysregulated apoptosis. Other enzymes in the DGK family have been associated with pigmentation and melanogenesis, for example DGKζ is implicated in modulation of tyrosinase levels.[42]

DUSP27

Members of the dual-specificity phosphatase (DUSP) family inactivate target kinases by removing phosphates from tyrosine, serine and threonine residues. Downstream signalling of DUSPs impacts a variety of MAP kinases, and therefore they have been proposed as novel targets in glioblastoma

and breast cancer therapy.[43, 44] Specific DUSPs have been associated with other cancers, including hepatocellular (DUSP28) and lung (DUSP6) cancer, as well as an in vivo role of DUSP5 as a tumour suppressor in skin cancer.[45-47] A novel missense mutation was identified in *DUSP27* in the 3-case subgroup of family 010482, at position chr1:167096580 (c.2212A>G; NM_001080426), resulting in p.Lys738Glu. In melanoma tumour samples, the somatic mutation frequency of *DUSP27* ranges from 4-20%.[48] Although the effects of *DUSP27* are still poorly understood, relevance of other DUSPs to cancer suggests that *DUSP27* may contribute to similar tumorigenic pathways.[49, 50]

SOX1

The novel variant 1139_1144insCACGCC in *SOX1* inserts two extra amino acids, but does not induce a frameshift. In melanoma tumour samples, no *SOX1* mutations have been reported.[21] However, it is overexpressed in many other cancer cell lines, and it suggested that SOX1 acts as a tumour suppressor by interfering with Wnt/β-catenin signalling in cervical cancer, nasopharyngeal carcinoma, and hepatocellular carcinoma.[51-53] It is also proposed to act as a tumour suppressor in NSCLC by regulating actin remodelling in the cytoskeleton, thereby inhibiting cell migration.[54] Although *SOX1* may be relevant in other cancers, at this stage the lack of existing melanoma mutations and the nonframeshift nature of this variant means that it seems less likely to contribute to melanoma in this family.

PARK7

The four case sub-group had a segregating novel missense substitution p.Ala29Gly (c.86C>G) in *PARK7*, which codes for a cancer and Parkinson's disease related protein that protects cells from oxidative stress via multiple pathways.[55] *PARK7* is overexpressed in a variety of different tumours – with clinical impact as a diagnostic or prognostic biomarker in NSCLC, breast cancer, bladder cancer, laryngeal SCC, and papillary thyroid cancer, as well as roles in cell differentiation, migration, or proliferation in acute leukaemias and pancreatic cancer.[55-58] Via interactions with the protein BBS1, it has also been associated with mesothelioma.[59] Effectors of PARK7 signaling include the PI3K/AKT pathway, the MAPK pathway, and p53, and it is possible that mutations in *PARK7* could drive melanomagenesis through these downstream mechanisms.

Table 8b: Rare variants of interest in bilineal family 010482										
	Overall group									
	APC		**ARID1B**		**AXIN1**		**BRIP1**		**MSH6**	
	AA	rs number	AA	rs number	AA	rs number	AA	rs number	AA	rs number
005977	WT		E652D	rs139125255	WT		WT		L266V	rs2020908
010482	WT		E652D	rs139125255	WT		V193I	rs4988346	WT	
011982	S2603C	rs72541816	WT		WT		V193I	rs4988346	WT	
022591	S2603C	rs72541816	WT		WT		WT		L266V	rs2020908
023479	WT		E652D	rs139125255	D495E	rs146947903	V193I	rs4988346	WT	
	3 case group									
	CKAP2		**HUS1**		**APC**		**MSH6**			
	AA	rs number	AA	rs number	AA	rs number	AA	rs number		
005977	E518K	rs41292820	D269N	rs10253916	WT		L266V	rs2020908		
010482										
011982	E518K	rs41292820	D269N	rs10253916	S2603C	rs72541816	WT			
022591	E518K	rs41292820	D269N	rs10253916	S2603C	rs72541816	L266V	rs2020908		
023479										
	4 case group									
	MAP3K11		**ARID1B**		**BRIP1**					
	AA	Allele frequency	AA	rs number	AA	rs number				
005977	C2519T	0.000117	E652D	rs139125255	WT					
010482	C2519T	0.000117	E652D	rs139125255	V193I	rs4988346				
011982	C2519T	0.000117	WT		V193I	rs4988346				
022591										
023479	C2519T	0.000117	E652D	rs139125255	V193I	rs4988346				
3 case: two affected children and their father; 4 case: two affected children, their mother, and their maternal uncle AA: amino acid change, rs: reference SNP										

Rare segregating variants:

CKAP2

The rare missense mutation p.Glu518Lys (c.1552G>A, rs41292820) changes glutamic acid to lysine in exon 8 of *CKAP2*, and is designated as damaging by SIFT and probably damaging by PolyPhen2. Although infrequently mutated in melanoma (1-2%), somatic alterations in CKAP2 are associated with other cancers, and CKAP2 expression may offer prognostic information for breast and liver cancer.[48, 60, 61]

HUS1

This family had a segregating rare variant p.Asp269Asn (c.805G>A, rs10253916) in *HUS1*, a gene that encodes a checkpoint protein. Hus1, with the other checkpoint sensors Rad9 and Rad1, forms the 9-1-1 heterotrimeric complex. This complex is involved in DNA damage repair not only by sensing DNA damage, but also via downstream effects on base excision repair.[62] *HUS1* polymorphisms have been suggested as low penetrance risk alleles for differentiated thyroid cancer, as well as for familial breast and ovarian cancer.[63, 64]

MAP3K11

The gene product of *MAP3K11*, MLK3, is a signal integrating kinase that directly phosphorylates and activates the JNK pathway, and may also regulate RAF/ERK signalling. A rare variant in *MAP3K11* (c.2519C>T, p.Pro840Leu) segregated with melanoma in all affected family members. Germline *MAP3K11* variants have been associated with survival after colon cancer in a case-control study, and a role for MAP3K11 as a tumour suppressor has been suggested in cell line studies of B-cell leukaemia and prostate cancer.[65-67]

012081

Novel segregating mutations were found in *SETD5* and *TP53BP1*, along with non-segregating mutations in *APC2*, *MAP3K4*, *PALB2*, and *SLX4* (Figure 12, Table 9a, Table 9b). Non-segregating mutations were also detected in *ANKRD17* and *BARD1*, which encode BAP1 interacting partners. Rare non-segregating mutations were seen in *TERT*, *ARID5A*, *AXIN2*, *DNMT3B*, and *MLH1*.

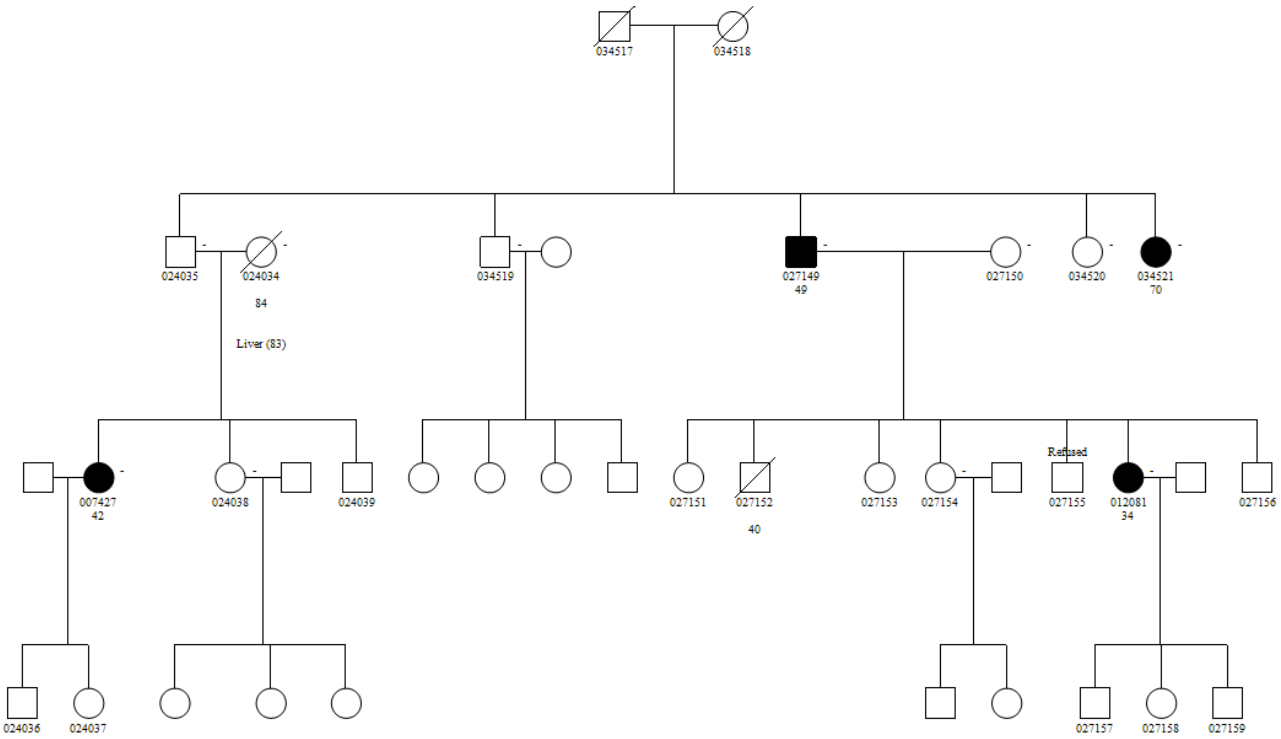

Figure 12. Pedigree of family 012081

Table 9a: Novel variants of interest in family 012081								
	SETD5	**TP53BP1**	**ANKRD17**	**BARD1**	**APC2**	**MAP3K4**	**PALB2**	**SLX4**
007427	L601V	nfsins	WT	S212F	WT	F495S	WT	H955P
012081	L601V	nfsins	WT	WT	WT	WT	L402V	WT
034521	L601V	nfsins	Q1873R	WT	R2008G	WT	WT	WT
nfsins: non-frameshift insertion								

Table 9b: Rare variants of interest in family 012081										
Gene:	**TERT**		**ARID5A**		**AXIN2**		**DNMT3B**		**MLH1**	
	AA change	rs number	AA change	rs number	AA change	rs number	AA change	rs number	AA change	rs number
007427	WT		G194E	rs150396730	WT		A417V	rs116943489	WT	
012081	WT		WT		L662P	rs142476324	WT		V647M	rs35831931
034521	V791I	rs141425941	G194E	rs150396730	WT		WT		V647M	rs35831931
AA: amino acid, rs: reference SNP										

Novel segregating variants:

SETD5

Although *SETD5* has been most consistently associated with intellectual disability, it has also been recently identified as a novel biomarker in prostate cancer.[68, 69] In a set with four other markers, SETD5 has been proposed to enable recognition of aggressive prostate cancer, although by unknown mechanisms.[68] In melanoma tissue samples, *SETD5* has a somatic mutation frequency ranging from 4-15%, and is infrequently mutated in tissue samples in the COSMIC database.[21, 48] It is therefore difficult to determine the possible contribution of the novel missense mutation, p.Leu601Val, to melanoma aggregation in this family.

TP53BP1

TP53BP1 mediates DNA double-strand break repair by processing the DNA damage response signal and recruiting other repair proteins. A nonframeshift deletion, c.1363_1368delCCTATC, segregated in all members of this family, and *TP53BP1* has a mutation frequency in melanoma ranging from 3-16%.[48] While studies on 53BP1 staining in melanoma cells have been inconclusive, TP53BP1 expression in thyroid papillary microcarcinoma has been associated with BRAF V600E mutation status, a known somatic driver of melanoma.[70, 71] TP53BP1 also interacts with BRCA1, another gene product linked to melanoma, and reduced expression of *TP53BP1* is strongly correlated with triple-negative breast cancer and *BRCA1*-mutated breast cancers.[72] Unlike the findings in breast cancer, *BRCA1*-mutated ovarian carcinomas have higher 53BP1 protein expression than wildtype cancers.[73] Other cancers linked to *TP53BP1* include colorectal cancer, via effects on cell proliferation and apoptosis, as well as prostate cancer and pancreatic adenocarcinoma.[69, 74, 75]

012828

A novel mutation in *NEK7* segregated in all four family members affected by melanoma, including a male with three other non-melanoma cancers (Figure 13, Table 10a). Non-segregating novel mutations were found in *ERCC8*, *MAP3K13*, and *TBX2*, as well as a rare non-segregating mutation in *ARID4A* (Table 10b). Other cancers in this family include prostate, parotid, and breast cancer in a male affected by melanoma, NSCLC in his brother who was also affected by melanoma, and CRC and lymphoma in their sister.

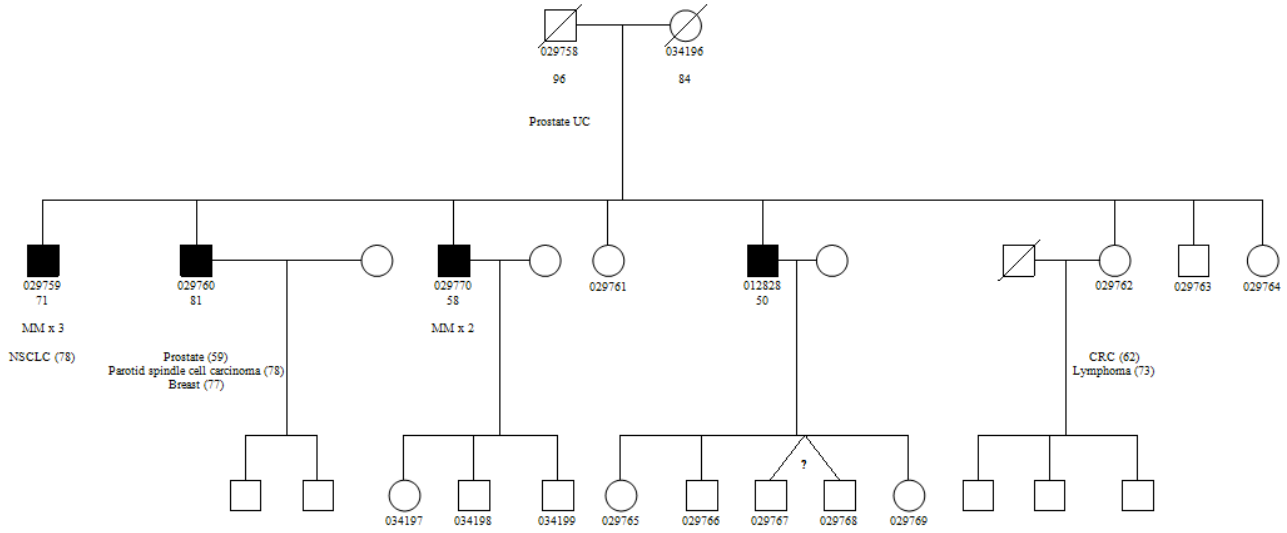

Figure 13. Pedigree of family 012828

Table 10a: Novel variants of interest in family 012828				
	NEK7	**ERCC8**	**MAP3K13**	**TBX2**
012828	splicing	WT	WT	WT
029759	splicing	WT	WT	WT
029760	splicing	S138N	R385Q	WT
029770	splicing	S138N	WT	G527R

Table 10b: Rare variants of interest in family 012828				
Gene:	**ARID4A**		**BRIP1**	
	AA change	rs number	AA change	rs number
012828	WT		R173C	rs4988345
029759	WT		WT	
029760	splicing	rs62621193	WT	
029770	splicing	rs62621193	R173C	rs4988345
AA: amino acid, rs: reference SNP				

NEK7

In this family, a splicing A>G variant of *NEK7* segregated in all individuals. *NEK7* has not been previously associated with melanoma, and is mutated in less than 1% of melanoma tumour samples.[48] However, it is variably expressed in a number of other tumour types, being overexpressed in 10% or more of adrenal, breast, liver, and ovary tissue samples.[21] *NEK7* has also been linked to gallbladder carcinoma differentiation and metastasis.[76] The gene product is associated with cell cycle control, and along with NEK2 and NEK9, contributes to establishing the microtubules of the mitotic spindle for cell division.[77] Reduction of NEK7 has been shown to arrest cells in mitosis, and therefore has important consequences for cell growth and survival.[78]

013049

No segregating variants were identified in this 6-case family, although novel non-segregating mutations in *DCC*, *GNAS*, *MAP3K1*, *POLE*, *RAD52*, *ROS1*, and *TET2* were found in some family members (Table 11a). *POLE* has recently been implicated in familial melanoma after a novel variant was found in a 7-case melanoma family, and is also proposed to predispose to a wider spectrum of cancers.[79] Rare non-segregating mutations were found in *BRCA1, BRCA2, SOX13, SOX4, FANCI,* and *WWOX* (Table 11b). One male affected by melanoma also had prostate cancer and mesothelioma, however no sample was available for testing. In first degree relatives of melanoma cases, other cancers included lung, prostate, and colorectal cancer (Figure 14).

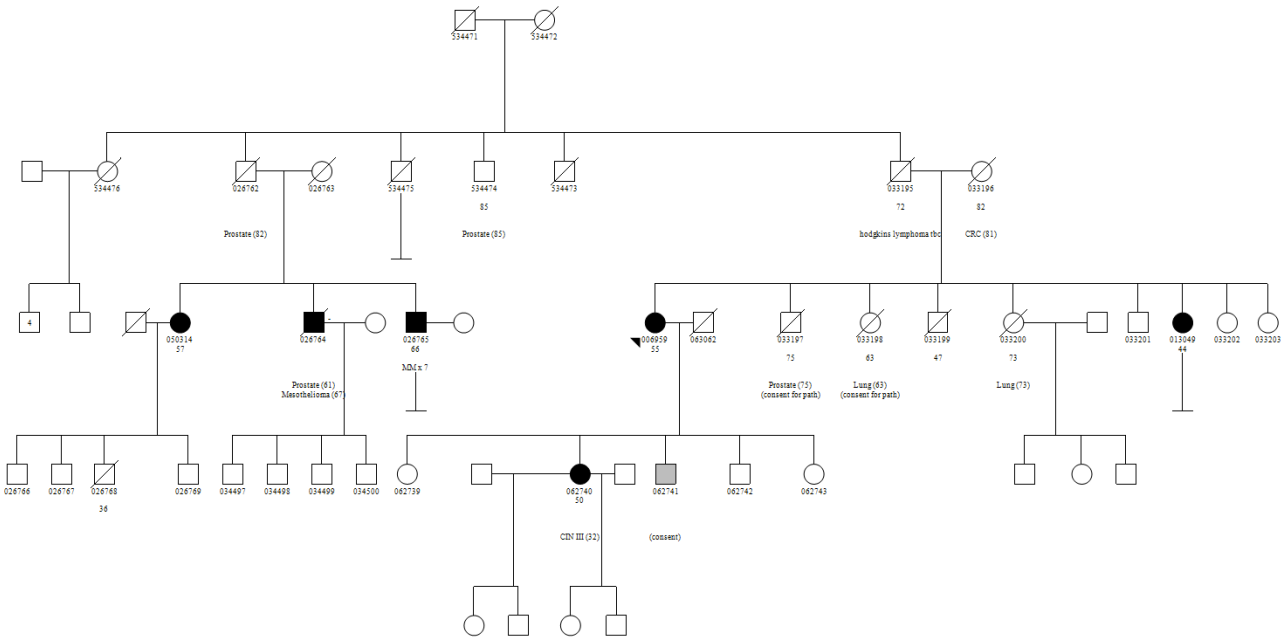

Figure 14. Pedigree of family 013049

Table 11a: Novel variants of interest in family 013049							
	DCC	**GNAS**	**MAP3K1**	**POLE**	**RAD52**	**ROS1**	**TET2**
013049	WT	WT	WT	WT	WT	WT	WT
026765	G1055S	WT	WT	WT	V240G	I431V	WT
062740	WT	P379L	A140S	R266Q	WT	WT	WT
050314	G1055S	WT	WT	WT	WT	I431V	Q526X

Table 11b: Rare variants of interest in family 013049						
Gene:	**BRCA1**		**BRCA2**		**SOX13**	
	AA change	rs number	AA change	rs number	AA change	rs number
013049	N1189K	rs28897687	A2951T	rs11571769	R377H	rs201772428
026765	WT		A2951T	rs11571769	R377H	rs201772428
062740	WT		WT		WT	
050314	WT		C1151T	rs41293475	WT	
Gene:	**SOX4**		**FANCI**		**WWOX**	
	AA change	rs number	AA change	rs number	AA change	rs number
013049	WT		WT		WT	
026765	L28V	rs140231408	WT		WT	
062740	WT		V1176I	-	L159F	rs186745328
050314	WT		WT		WT	
AA: amino acid, rs: reference SNP						

050904

A segregating mutation in *ERCC3* was observed, as were segregating rare mutations in *ABCB5* and *MUTYH* (Table 12a, Table 12b). Non-segregating mutations were found in *SLX4* and *NF1* (novel variants), and *CDKN2A, TP53BP2,* and *XRCC4* (rare variants). Three melanoma cases were affected by additional cancers, including breast cancer, myeloma, and lymphoma (Figure 15).

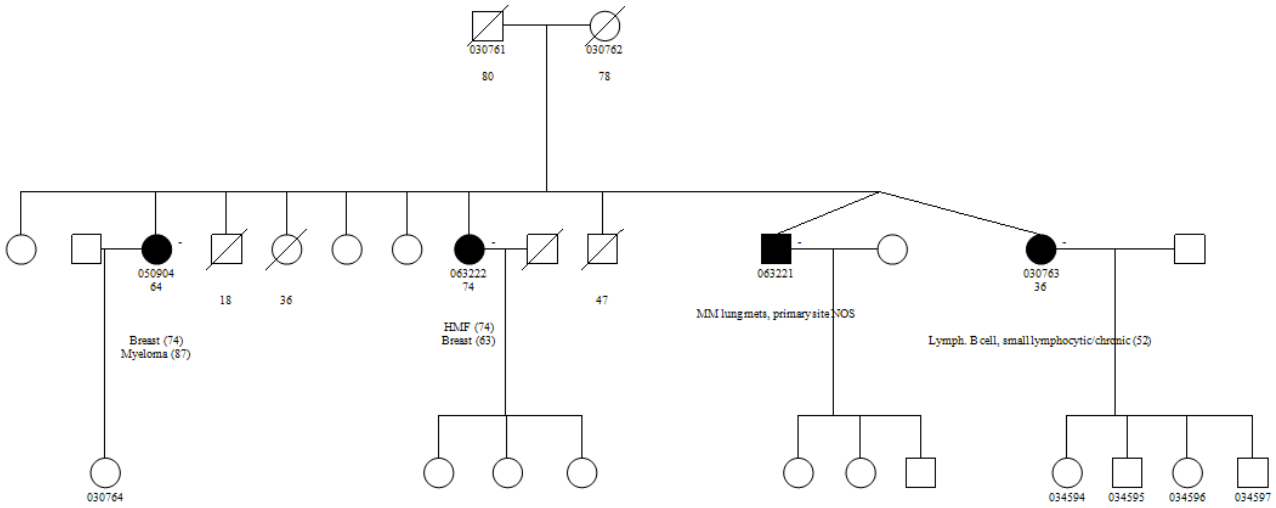

Figure 15. Pedigree of family 050904

Table 12a: Novel variants of interest in family 050904		
	ERCC3	**SLX4**
030763	fsdel	WT
050904	fsdel	R310Q
063221	fsdel	WT
063222	fsdel	WT
fsdel: frameshift deletion		

Novel segregating variants:

ERCC3

The *ERCC3*/*XPB* gene codes for xeroderma pigmentosum type B (XPB), a DNA helicase that contributes to the general transcription factor IIH (TFIIH) complex. It is suggested that XPB acts to unwind and hold open strands of DNA to enable nucleotide excision repair, and therefore a mutation in this gene may impact the ability of cells to repair DNA damage.[80, 81] The variant identified in this family, c.1618delA, induces a frameshift from the single nucleotide deletion in the ERCC3/RAD25/XPB C-terminal helicase. The frameshift changes the amino acid lysine to asparagine at position 540, as well as six subsequent amino acid changes before truncating the protein with a TGA opal stop codon at position 547.[21] 1-5% of melanoma samples have mutations in *ERCC3*, and a handful of rare germline mutations in *ERCC3* have been associated with xeroderma pigmentosum.[48, 82] Previously detected mutations in XPB/ERCC3 include two functionally relevant amino acid substitutions and six frameshift/protein truncations, and it is possible that the novel frameshift mutation p.Lys540Asn could increase skin cancer susceptibility in this family through compromised repair of DNA damage.

Table 12b: Rare variants of interest in family 050904										
Gene:	**ABCB5**		**MUTYH**		**CDKN2A**		**TP53BP2**		**XRCC4**	
	AA change	rs number	AA change	rs number	AA change	rs number	AA change	rs number	AA change	rs number
30763	splicing	rs193255587	G382D	rs36053993	G63R	rs45456595	R83C	rs200028775	L75S	rs61762970
50904	splicing	rs193255587	G382D	rs36053993	WT		WT		L75S	rs61762970
63221	splicing	rs193255587	G382D	rs36053993	G63R	rs45456595	R83C	rs200028775	L75S	rs61762970
63222	splicing	rs193255587	G382D	rs36053993	G63R	rs45456595	WT		WT	
AA: amino acid, rs: reference SNP										

Rare segregating variants:

ABCB5

ABCB5 encodes for ATP-binding cassette, sub-family B (MDR/TAP), member 5 (ABCB5), a plasma protein efflux transporter that helps maintain the cell membrane in a hyperpolarised state.[83] Via these effects on the cell membrane, ABCB5 was initially demonstrated to regulate physiologic progenitor cell fusion in melanocytes.[83] Beyond its presence at low levels in normal skin, ABCB5 has also been associated with melanoma. Malignant subpopulations of melanoma-initiating cells have been shown to express ABCB5, impacting cell fusion of stem cells and subsequent potential for differentiation and progression. A role in immunomodulation has been recently demonstrated, where ABCB5 may identify dermal immunoregulatory cells.[84] It has also been assessed as a biomarker of circulating tumour cells in peripheral blood, and is associated with melanoma recurrence.[85] Another key effect of ABCB5 expression is chemoresistance. As a multi-drug resistance transporter, ABCB5 has the ability to regulate passage of drugs into the cell, and it induces resistance to melanoma treatment by the direct efflux of multiple chemotherapy agents.[86-88] Chemoresistance inferred by ABCB5 has been identified in other cancers, namely liver cancer and hepatocellular cancer.[89-91] A possible role has also been proposed in oral SCC and leukaemia, and it is overexpressed in almost a third of sporadic oesophageal cancer.[21, 92, 93] The rare segregating variant in this family (rs193255587) is a splicing mutation, and the effects of this mutation would depend on consequent protein expression and function.

MUTYH

A rare missense mutation in the NUDIX domain of *MUTYH* was detected (p.Gly382Asp, rs36053993), designated as damaging by both SIFT and PolyPhen2. *MUTYH* is a base excision repair gene, with strong links to CRC. While the highest risk of CRC is for carriers of two mutated *MUTYH* alleles, which results in carriers having *MUTYH*-associated polyposis. CRC risk also appears elevated for monoallelic carriers.[94]

051656

Novel variants in *MACF1, MX2* and *TNK2* segregated in all four melanoma cases, as well as five other segregating rare variants in *FANCI*, *PML*, *SLK*, and *WWOX* (Table 13a, Table 13b). A rare segregating variant was also identified in *KDM1B*, encoding a gene product known to be associated with BAP1. Non-segregating novel variants were noted in *ERCC3*, *DCC*, *ERBB4*, and *RBL1*, and non-segregating rare variants in *BRCA1* and *BUB1*. One male first degree relative had bladder cancer (Figure 16).

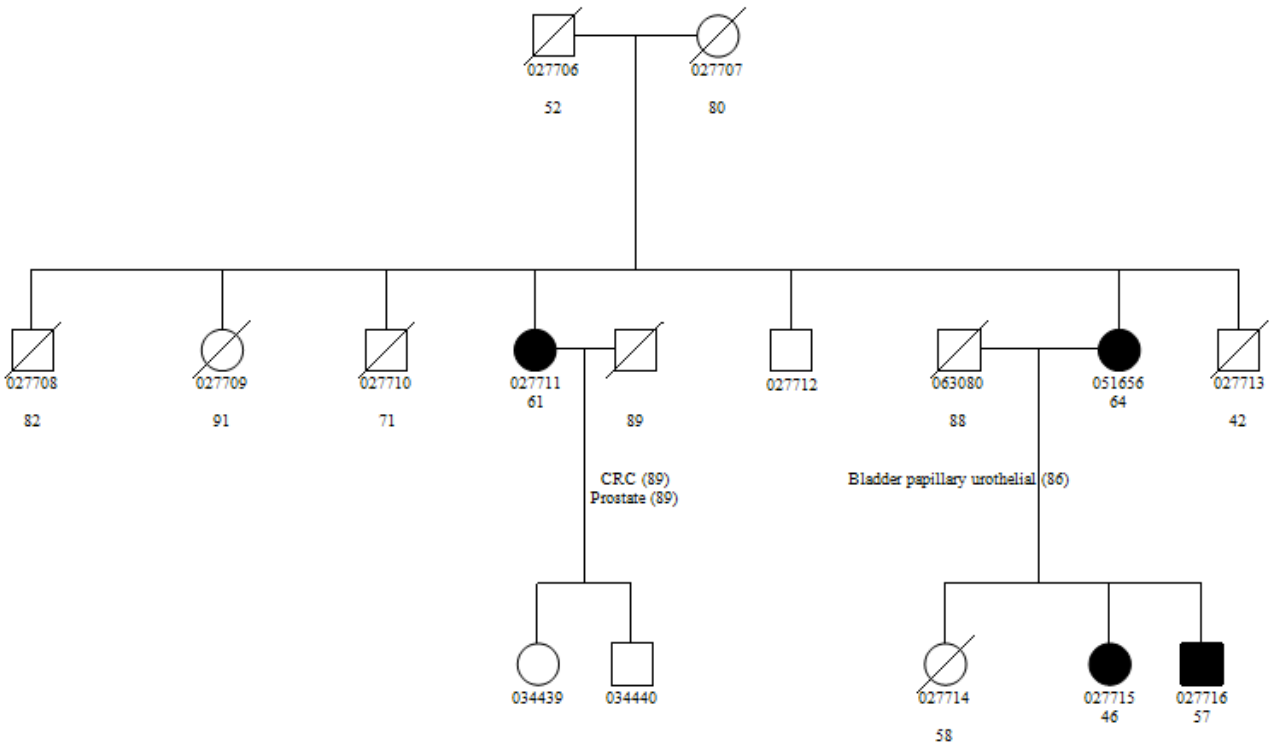

Figure 16. Pedigree of family 051656

Table 13a: Novel variants of interest in family 051656							
	MACF1	**MX2**	TNK2	**ERCC3**	**DCC**	**ERBB4**	**RBL1**
27711	R415Q	R593X	P7R	WT	WT	WT	C918R
27715	R415Q	R593X	P7R	fsins	A1250T	R992H	WT
27716	R415Q	R593X	P7R	fsins	A1250T	WT	WT
fsins: frameshift insertion							

Novel segregating variants:

MACF1

MACF1 encodes proteins that are able to form bridges between different cytoskeletal elements, and their impact on dynamic microtubule and actin organisation has the capacity to influence cell migration, vesicular trafficking, and axonal extension.[95] *MACF1* mutations have been rarely described in cancer, however it has been described in a case of neuroblastoma, where a chromosome 1p breakpoint disrupted the gene.[96] Additionally, APC-directed recruitment of MACF1 to the plasma membrane and subsequent microtubule stability has been implicated in breast cancer cell motility.[97] *MACF1* mutation frequency ranges from 8-14% in cutaneous melanoma, and is reported as 40% in desmoplastic melanoma. It is plausible that the p.Arg415Gln mutation (c.1244G>A) found in this family may contribute to motility and migration of cancer cells.[48]

MX2

The nonsense mutation Arg593* (c.1777C>T) creates a stop codon at the variant site, truncating the interferon-induced GTP-binding protein, MX2. MX2 is in the family of large dynamin-like GTPases, and in addition to roles in HIV-1 suppression and antiviral activity, it has also been connected with melanoma.[98-100] The *MX2* SNP rs45430 has recently been significantly associated with multiple primary melanoma, subsequent to its identification through GWAS in 2011 as a new melanoma susceptibility locus.[98, 100] As MX2 exerts antiviral activity on HIV-1 through effects on nuclear uptake and delaying G(1)/S cell cycle progression, it is plausible that the impact of *MX2* mutation in melanoma may be related to similar processes of cell transport and cell cycle regulation.[101]

TNK2

The *TNK2* gene (also called *ACK1*) encodes for a non-receptor tyrosine kinase, activated CDC42 kinase 1 (ACK1), that is upregulated in many cancers and promotes cancer progression.[102] Further to its role relaying extracellular signals from RTKs to their intracellular effectors, *TNK2*/*ACK1* has been discovered as an epigenic regulator, and has interactions that promote downstream growth of gastric cancer, hepatocellular cancer, tamoxifen-resistant breast cancer, leukaemia, and prostate cancer.[102-105] Overexpression of *TNK2*/*ACK1* has been noted in a range of additional cancers, including cervical, ovarian, lung, and upper digestive.[21, 48] A novel missense mutation, p.Pro7Arg, is found near the start of the sterile α motif domain of TNK2/ACK1. Although infrequently mutated in melanoma tissue samples (3-5%), the range of cancers impacted by *TNK2*/*ACK1* suggests that the variant may contribute to cellular processes in melanoma progression.[48]

Table 13b: Rare variants of interest in family 051656								
Gene:	**FANCI**		**KDM1B**		**PML**		**SLK**	
	AA change	rs number	AA change	rs number	AA change	rs number	AA change	rs number
27711	T824C	rs142906652	S252P	rs138145635	Q668R	rs140648301	E821K	rs140813954
27715	T824C	rs142906652	S252P	rs138145635	Q668R	rs140648301	E821K	rs140813954
27716	T824C	rs142906652	S252P	rs138145635	Q668R	rs140648301	E821K	rs140813954
Gene:	**WWOX**		**BRCA1**		**BUB1**			
	AA change	rs number	AA change	AA change	rs number	AA change		
27711	R7W	rs141361080	S1465I	rs1800744	A206V	rs61730706		
27715	R7W	rs141361080	WT					
27716	R7W	rs141361080	WT					
AA: amino acid, rs: reference SNP								

Rare segregating variants:

FANCI

A missense mutation in *FANCI*, p.Ile275Thr (rs142906652), segregated in all family members, and was designated as damaging by both SIFT and PolyPhen2. *FANCI* is part of the Fanconi anaemia complementation group, comprising multiple genes associated with DNA repair. Partnered activity of FANCI and BRCA1 (also known as FANCD2) has an essential role in DNA damage repair, however it has recently been suggested that FANCI alone is sufficient for formation of Fanconi anaemia core complex foci.[106] Although its independent effects mean it is less likely to be a *BRCA1* phenocopy, deleterious germline mutations in *FANCI* have been noted in breast cancer.[107]

KDM1B

The *KDM1B* gene product interacts with BAP1, and thus the segregating rare missense mutation p.Ser252Pro (rs138145635) in *KDM1B* may contribute to a cancer phenotype reminiscent of that seen in families with mutated *BAP1*. The protein is a histone lysine demethylase, and is part of a subnetwork that overlaps the BAP1 complex.[108] Interestingly, a rare non-segregating mutation in *BRCA1* was also noted in this family.

PML

A segregating missense mutation p.Gln668Arg (rs140648301) was found in *PML*, a gene located at 15q24.1 that encodes the PML tumour suppressor protein. PML is a key component of dynamic nuclear structures termed PML-nuclear bodies, which function as regulators of transcription, cell cycle control, DNA damage response, and apoptosis. The implication of disrupted *PML* is demonstrated by the t(15;17) translocation of acute promyelocyctic leukaemia (APL), generating the consequent oncogenic fusion protein PML-retinoic acid receptor-alpha.[109] Studies in mice assessing the relationship between mutated *p53* and *PML* found enhanced accumulation of mutant p53 in the absence of PML, accompanied by development of lymphomas and sarcomas.[109] Loss of PML function via a damaging mutation like p.Gln668Arg may therefore promote oncogenesis by removing the brakes from other ‘gain of function’ mutations.

SLK

SLK encodes for the Ste20-like kinase SLK, a serine/threonine protein kinase that mediates apoptosis and may impact cell migration via effects on cytoskeleton disassembly.[110] SLK is expressed in a range of normal tissue, and has also been identified as a downstream effector of chemotaxis in ErbB2 activated breast cancer cell lines. It is possible that the segregating missense mutation p.Glu821Lys (rs140813954) could add to polygenic risk in conjunction with the multiple additional mutations in this family.

WWOX

WWOX spans the common chromosomal fragile site FRA16D, a region of chromosomal instability that is particularly sensitive to replicative stress. Consistent with other genes located at fragile sites, *WWOX* has been recognised as a tumour suppressor gene, and its loss has effects on multiple signalling pathways including DNA damage response and apoptosis. Cancer associations for germline *WWOX* variants include susceptibility to prostate cancer, progression of head and neck cancers, and overall survival in pancreatic cancer.[111-113] A potential role has also been recognised in myeloma, where loss of heterozygosity at the location of *WWOX*, 16q23, led to reduced WWOX expression and worse overall survival.[114] In this family, a missense mutation in *WWOX* (p.Arg7Trp, rs141361080) was found to be damaging by both SIFT and PolyPhen2. Although this gene has not previously associated with melanoma, links with tumour progression in multiple other cancers may hint at a potential pleiotropic effect.

052448

Three segregating mutations were found in this family: a novel variant in *GRIN2C*, and two different rare variants in *TYRP1* that may represent a single haplotype (Figure 17, Table 14a, Table 14b). A novel non-segregating mutation was found in *ASXL2*, encoding a BRCA1-associated protein in addition to non-segregating novel variants in *ALK*, *ARID3A*, *ARID4B*, *DGKB*, *JAK2*, *MLH3*.

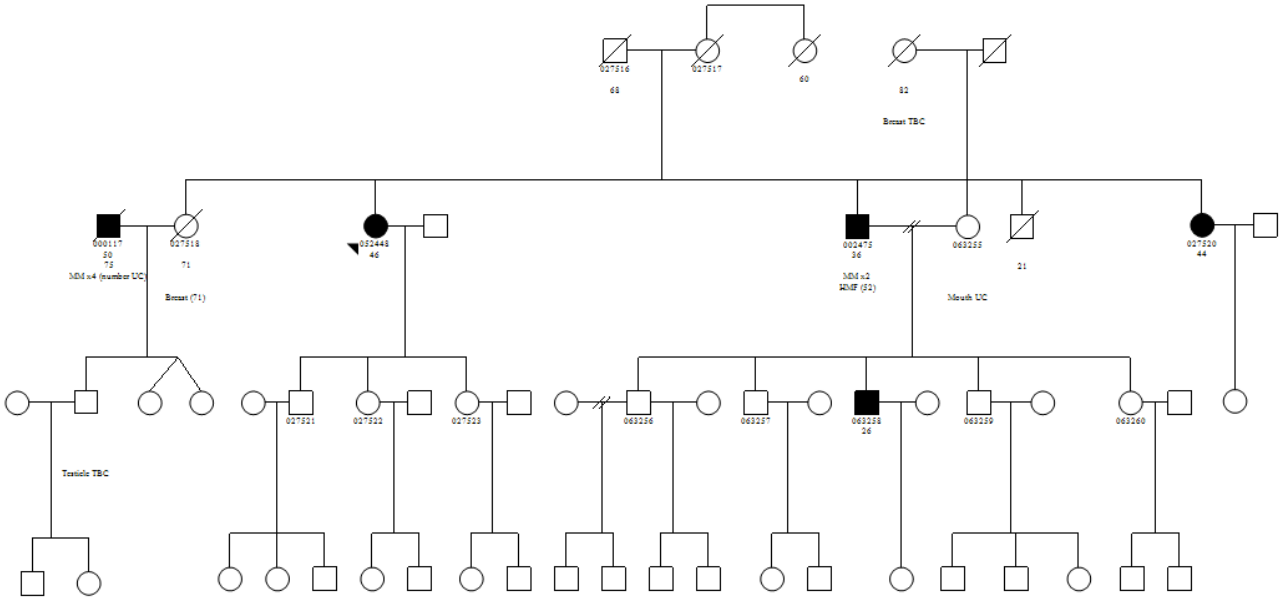

Figure 17. Pedigree of family 052448

Table 14a: Novel variants of interest in family 052448								
	GRIN2C	**ALK**	**ARID3A**	**ARID4B**	**ASXL2**	**DGKB**	**JAK2**	**MLH3**
27520	nfsins	D1141N	A429T	nfsdel	WT	WT	H891Y	R1152C
52448	nfsins	WT	A429T	WT	W213R	V98I	WT	R1152C
63258	nfsins	D1141N	WT	WT	WT	V98I	WT	WT
nfsdel: non-frameshift deletion, nfsins: non-frameshift insertion								

Novel segregating variants:

GRIN2C

GRIN2C encodes the glutamate (NMDA) receptor subunit NMDAR2C, and the nonframeshift insertion c.3138_3146insCCCAGAGCC results in an additional three amino acids. Mutations in this gene have previously been associated with neuromuscular effects, and mutation frequency in melanoma ranges from 2-8%.[48] A paralog, *GRIN2A*, has been identified as frequently mutated in melanoma, however it is possibly due to divergent effects on downstream MAPK signalling rather than a shared mechanism with *GRIN2C* (Wei 2011, Willard 2013).[115, 116]

Table 14b: Rare variants of interest in family 052448

Gene:	**TYRP1**		**TYRP1**	
	AA change	rs number	AA change	rs number
27520	A24T	rs61758405	R153C	rs146027807
52448	A24T	rs61758405	R153C	rs146027807
63258	A24T	rs61758405	R153C	rs146027807
AA: amino acid, rs: reference SNP				

Rare segregating variants:

TYRP1

Two rare damaging *TYRP1* variants segregated in this family, p.Ala24Thr (rs61758405) and p.Arg153Cys (rs146027807), inferring a bi-allelic haplotype. *TYRP1* has important functions in melanin synthesis and also in maintaining stability of the tyrosinase protein. The spectrum of mutation phenotype ranges from oculocutaneous albinism and Melanesian blonde hair in those with homozygous or compound heterozygous TYRP1 mutations, to fairer skin, eye, and hair colour in heterozygous carriers.[117, 118] Similar to *MC1R*, *ASIP*, and *TYR* polymorphisms, some variants in *TYRP1* are associated with fair pigmentation phenotypes, and have been associated with cutaneous melanoma.[119-121] Several *TYRP1* germline variants have recently been associated with multiple primary melanoma.[100]

BAP1 phenocopies

Further to the genes above, a number of variants were identified in genes that encode products which interact with that of the known melanoma predisposition gene, *BAP1*. The tumour suppressor function of BAP1 is in part due to ubiquination, mediated by coordinated activity between BAP1 and the BRCA1/BARD1 complex.[122] The integration of multiple proteins is evident from studies in mice, where BARD1 deficiency led to phenotypes similar to those expressed in *BRCA1* mutations. A novel *BARD1* mutation was noted in family 012081, in addition to *BRCA1* and *BRCA2* variants in family 007178 and 013049. BAP1 also has links with ASXL1, where together they form the Polycomb group repressive deubiquitinase complex.[123] Cell senescence is also regulated by an interaction with ASXL2, although ASXL1 appears more deleterious when mutated.[124] A novel *ASXL1* variant was detected in family 007178, and in addition to possible melanoma predisposition, mutations in *ASXL1* have been significantly associated with haematological malignancies. *ANKRD17* and *KDM1B* are also associated with the BAP1 complex, and mutations in these genes were found in family 012081 and 051656 respectively, with the *KDM1B* mutation segregating in all family members.[108] Through their interactions with BAP1, it is proposed that these associated genes impact similar pathways, and thus a mutation in one of these genes may have the same phenotypic outcome as BAP1 mutations in predisposing to melanoma and other cancers.

Excluded variants

Variants with counts higher than the number of affected members in each family were excluded, to account for the possibility of these variants representing copy errors rather than a true mutation. Excluded variants were *ARID1B, GNAL, KISS1, MNT,* and *XRCC1*. *ARID1B* variants were observed in many families, with some variants appearing to segregate or partially segregate. Due to the number of *ARID1B* variants we have excluded this variant due to the possibility of copy errors.

Novel and rare variants in individuals with three or more cancer types

Four females and seven males with three or more invasive cancers including melanoma had DNA samples available for sequencing (Table 15).

Table 15 Results of next generation sequencing for individuals affected by melanoma and at least two other invasive cancers

Family	Indiv ID	Seq	Cancers in order of diagnosis	Novel variants	Rare variants
Females					
005921	031531	WES	Melanoma, CLL, NHL	MAP3K1, MAP3K13, MAP3K4	BRCA2, FANCC
011734	001043	WES	Melanoma x 4, Endometrial, Thyroid	APC, MAGI1, NEK4	MC1R, RET
050657	050657	WGS	Melanoma, Myeloma, CML	ALK, FANCD2	ASXL2, BAP1, CDKN2A, FANCC, FANCG, MAP3K10, MAP4K3, TERT
050904	050904	WGS	Melanoma, Breast, Myeloma	APC, ERCC3, MAP3K4, MSH2, NF1, POLD1, SLX4	APC, BARD1, CBLB, ERBB3, MLH3, OCA2, POLD1, RAD51C, RET, XRCC4
Males					
002145	016018	WES	Thyroid, Melanoma, RCC	MAP2K3, MAP3K4, MAP3K6	(none)
003091	003091	WES	RCC, Prostate, Melanoma	FANCA, FANCC	FANCI, MAP3K10, MAP4K3, RAD51C, TET2
009782	009782	WES	Melanoma, CRC, AML	APC, ARID5B, PLK5, TET2, TP53AIP1	BARD1, BCR, CBLB, EDNRB, FANCC, TET2
012828	029760	WES	Prostate, Breast, Parotid, Melanoma	MAGI1, MAP3K13, MAP3K5, NEK7, PLK5	ARID4A
013398	013398	WGS	Melanoma, NHL, RCC, CRC, Prostate	CDH1, ETV5, MAP3K4, POLD1	FANCC, FANCF, PML, POT1
050492	050492	WGS	Melanoma, Prostate, NHL, CLL	CDH1, IDH1	ERCC6L2, ERCC8, XRCC5
050695	050695	WGS	Melanoma x4, CRC, Gallbladder	ARID3B, MC1R, MTAP	(none)

Indiv ID: individual ID, Seq: sequencing, AML: acute myeloid leukaemia; CLL: chronic lymphocytic leukaemia; CML: chronic myeloid leukaemia; CRC: colorectal cancer; NHL: non-Hodgkin lymphoma; RCC: renal cell carcinoma, WES: whole exome sequencing, WGS: whole genome sequencing.

Females

031531

A rare *BRCA2* variant and two frameshift mutations in MAPK pathway genes may have contributed to melanoma in this female, who subsequently developed CLL and NHL. Further to established *BRCA2* associations, the presence of a mutation in this gene may be particularly significant for this female due to a potential role for certain *BRCA2* variants in CLL predisposition.[125]

001043

This female was affected by multiple melanomas, and it is possible that a mutation in *MC1R* contributed to her developing four primary melanomas. She also had endometrial and thyroid cancer, and was found to carry mutations in two genes strongly associated with familial cancer – *RET* and *APC*. Germline mutations in the proto-oncogene *RET* are key to development and progression of familial medullary thyroid cancer, and it is proposed that low penetrance SNPs in this gene could also contribute to sporadic medullary thyroid cancer.[126] *APC* is also linked to multiple sporadic cancers, as well as familial adenomatous polyposis coli syndrome.

050904

This female with breast cancer and myeloma harboured mutations in several genes known to be associated with cancer, including a gene linked with breast cancer. Germline mutations in *RAD51C* have been identified in a small number of families with breast and/or ovarian cancer, and given existing associations between these cancers and melanoma for other genes, it is plausible that melanoma could be a pleiotropic effect of a germline mutation in *RAD51C*.[127] Her sister was also affected by both breast cancer and melanoma. Mutations in a number of genes linked with CRC susceptibility were identified (*APC*, *POLD1*, *MLH3*) as well as variants involved in DNA repair (*SLX4*, *XRCC4*). A novel frameshift mutation in *ERCC3* segregated in all melanoma affected members of her family, and it is possible that impaired DNA repair caused by the truncated gene product influenced oncogenesis. A non-segregating rare variant in *CDKN2A* was identified in her three relatives with melanoma, however she did not carry the mutation.

050657

This female was found to carry mutations in the high penetrance melanoma risk genes *BAP1*, *CDKN2A,* and *TERT*, as well as additional variants in genes related to Fanconi anaemia and MAPK pathways. While the presence of mutated *BAP1*, *CDKN2A*, and *TERT* certainly suggests a possible basis for her melanoma susceptibility, the presence of an *ALK* mutation is interesting in light of her

additional haematological cancers - myeloma and CML. Somatic mutations of *ALK* are associated with lymphoma, and expression of a novel *ALK* transcript from a de novo alternative transcript initiation site in intron 9 has recently been described in approximately 10% of melanomas.[128]

Males

016018

Following thyroid cancer, this male developed melanoma and RCC, however relatively few mutations in cancer genes were identified. He carried mutations in three MAPK pathway genes, including a *MAP3K4* frameshift variant, and these may have partially contributed to his cancer development.

003091

This male had RCC and prostate cancer, prior to developing melanoma. Sequencing demonstrated variants in DNA repair genes associated with the Fanconi anaemia pathway, which is implicated in melanoma as well as a diverse range of other cancers.[129, 130] A nonsense mutation was identified in *FANCC*, further to SNVs in *FANCA*, *FANCI*, and *RAD51C*.

009782

Although no melanoma predisposition gene variants were identified in this individual, a frameshift mutation in *TP53AIP1* may be significant in melanoma risk due to its likely role in mediating p53-dependent apoptosis. A *BARD1* mutation may also be significant, due to its function in mitotic spindle-pole assembly in conjunction with *BRCA1*. He additionally had a nonsynonymous SNV in *APC*, a gene associated with CRC, and a nonsynonymous SNV in *BCR*, which is associated somatically with ALL and CML via breakpoints in this gene that facilitate Philadelphia chromosome translocation. A frameshift mutation in *TET2* may have influenced the development of AML in this man, as somatic *TET2* mutations have been linked with myelodysplastic syndromes and leukaemias.[131] Although his sisters were not sequenced for possible mutations, development of breast cancer and CRC in one sister, and myeloma and melanoma in the other may have been influenced by the above variants.

029760

A diverse spectrum of cancers including melanoma, prostate, breast, and parotid cancer developed in this male, however few candidate predisposition genes were identified on sequencing. He carried mutations in two genes impacting cell cycle control – a segregating splicing variant in *NEK7*, and a

SNV in *PLK5*. *PLK5* has been identified as a potential tumour suppressor, due to silencing in astrocytoma and glioblastoma multiforme. He also had a splicing variant in *ARID4A*, which may have influenced melanoma development via effects of the gene product on retinoblastoma protein and subsequent cell proliferation. Of particular interest is his breast cancer, given the rarity of this cancer in males. No *BRCA2* or *BRCA1* mutations were identified, nor mutations in any genes known to interact with *BRCA1/2*.

013398

Five invasive cancers affected this male – melanoma, NHL, RCC, CRC, and prostate cancer. A strong familial component to cancer development is suggested by the presence of multiple cancers in his father, who was affected by two primary melanomas, Hodgkin lymphoma, and CML. It would be interesting to assess for potential shared germline variants in a father and son with an exceptionally high number of cancers, however his father had passed away and did not have any available DNA for sequencing. Mutations in two Fanconi anaemia pathway genes were noted, as well as mutations in *POT1* and *POLD1*. It is plausible that the variant in *POT1*, a known high penetrance melanoma susceptibility gene with links to other cancers, predisposed to a wider range of tumour types in this male and possibly also his father. The *POLD1* mutation may have contributed to an underlying CRC susceptibility. He also was found to carry mutated *PML*, a gene associated with acute promyelocytic leukaemia, which has also been tentatively linked to CML development.[132]

050492

This male had melanoma, prostate cancer, NHL, and CLL. Prostate cancer susceptibility has been suggested for carriers of a particular *CDH1* allele, and the gene has been implicated in hereditary diffuse gastric cancer and hereditary lobular breast cancer.[133-135] It is possible that this man's p.Pro6Arg mutation in *CDH1* contributed in a pleitropic manner to the development of multiple cancers.

050695

In addition to four primary melanomas, this man also had CRC and gallbladder cancer. A novel mutation in *MTAP* was noted, a gene located close to *CDKN2A* on chromosome 9p21.

Contribution of polygenic risk

For families with a high case density of melanoma, there were no segregating mutations in known high penetrance melanoma predisposition genes. As discussed in Chapter 2, a large proportion of melanoma families do not carry known risk genes, and therefore the balance of genetic susceptibility is proposed to fall almost entirely to a combination of low to moderate effect polymorphisms. Although it is unlikely that a SNP with low penetrance would alone lead to cancer, the combination of multiple risk SNPs in predictive models has promising ability to refine risk prediction in conjunction with pigmentation phenotype.[136] Beyond risk prediction, some melanoma loci have been implicated as novel biomarkers of melanoma recurrence and overall survival.[130, 137] The diverse phenotypes and different cancer 'syndromes' associated with particular 'melanoma' risk genes such as *BAP1* suggests a degree of pleiotropy, and hints at common pathways to oncogenesis. A recent study assessed 181 cancer-associated GWAS SNPs for possible risk associations with melanoma, and identified a pleiotropic effect for two lung cancer SNPs, and a male-specific effect for a prostate cancer SNP.[138] Given the wide range of genetic variants and also other cancer types in the cohort, it is plausible that some cancer-associated genes identified here also have pleiotropic effects in predisposing to melanoma.

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Chapter 5

Conclusion

Heritable melanoma risk is complex – comprised of possible known high penetrance genes, but more likely a mélange of low to moderate penetrance polymorphisms and co-modifiers that impact multiple pathways, each contributing to cancer in a small way with devastating impact when summated.

An over-representation in some cancer types detailed in chapter 3, coupled with the variety of cancer-associated genes identified in some families and individuals in chapter 4, hints at the possibility of common pathways for oncogenesis and pleiotropic effects for melanoma and cancer-associated risk genes.

Variable penetrance and rarity at the population level present challenges for the clinical application of familial cancer genetics. However, combination of novel SNPs in polygenic risk estimates has promising application in delineating disease risk and providing more sensitive estimates of prognosis. In melanoma, it is plausible that knowing of an unfavourable germline variant or set of variants may alter surveillance frequency and direct treatment choices toward a more aggressive approach at an earlier date, and improve clinical outcomes. It is also possible that novel variants predisposing to melanoma could identify pathways that may be amenable to targeted therapy in sporadic melanoma.

Overall, multiple genes and environmental modifiers likely modulate melanoma risk. In this cohort of Queensland 'intermediate risk' melanoma families, increased risk of some cancers has been identified at a population level, as well as numerous genes of interest in families with high case density and individuals with multiple cancers. Compared to the general cohort, it is interesting that some high case density families had few other cancers, whereas other high case density families had multiple additional tumour types including individuals with three or more different kinds of invasive cancer. Different sets of risk genes are likely to cause variable phenotypic expression, and also may be influenced by variable penetrance for different tumour types. The novel and rare segregating variants identified here in cancer-associated genes present promising candidate polymorphisms for familial melanoma.

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Appendix A: Novel segregating variants

AnnoGene	*Family*	*N fam*	*N var*	*chr*	*position*	*AnnoRegion*	*AnnoRefSeq*	*AnnoType*	*AnnoNTchange*	*AnnoAAchange*	*AnnoExon*
DGKA	010482_3	5	3	12	56335069	exonic	NM_001345	nonsynonymous SNV	G1135A	V379I	14
DUSP27	010482_3	5	3	1	167096580	exonic	NM_001080426	nonsynonymous SNV	A2212G	K738E	5
ERCC3	050904	4	4	2	128036858	exonic	NM_000122	frameshift substitution	1618_1621AAT		10
GRIN2C	052448	3	3	17	72839135	exonic	NM_000835	nonframeshift substitution	3138_3141CCCAGAGCCCCCG		13
MAGI1	007178	3	3	3	65425567	exonic	NM_001033057	nonframeshift substitution	1255_1257CATCAG		9
MAP4K4	007178	3	3	2	102488007	exonic	NM_145686	nonsynonymous SNV	G2479A	G827S	22
MCC	007178	3	3	5	112824068	exonic	NM_001085377	nonframeshift substitution	44_44delinsACGG		1
MX2	051656	3	3	21	42778797	exonic	NM_002463	stopgain	C1777T	R593X	13
NEK7	012828	4	4	1	198222168	splicing					
PARK7	010482_4	5	4	1	8022931	exonic	NM_001123377	nonsynonymous SNV	C86G	A29G	2
ROS1	007178	3	3	6	117631362	exonic	NM_002944	nonsynonymous SNV	G6316T	A2106S	40
SETD5	012081	3	3	3	9489388	exonic	NM_001080517	nonsynonymous SNV	C1801G	L601V	15
SOX1	010482_3	5	3	13	112723111	exonic	NM_005986	nonframeshift substitution	1139_1146CGGGCGTGGGCGTG		1
TP53BP1	012081	3	3	15	43762077	exonic	NM_001141979	nonframeshift substitution	1360_1368CCA		11
MACF1	051656	3	3	1	39750852	exonic	NM_012090	nonsynonymous SNV	G1244A	R415Q	11
TNK2	051656	3	3	3	195622268	exonic	NM_001010938	nonsynonymous SNV	C20G	P7R	1

N fam: number of individuals in the family. N seq: number of individuals sequenced. N var: number of variants identified in data set. Chr: chromosome. AnnoRegion: Genomic region as annotated by annovar. AnnoRefSeq: efSeq ID as annotated by annovar. AnnoType: Effect of mutation such as synonymous, nonsynonymous. AnnoNTchange: Nucleotide base change, AnnoAAchange: Amino Acid Change, AnnoExon: Exon number in transcript, SNV: single nucleotide variant.

Appendix B: Novel non-segregating variants

AnnoGene	*Family*	*N fam*	*N var*	*chr*	*position*	*AnnoRegion*	*AnnoRefSeq*	*AnnoType*	*AnnoNTchange*	*AnnoAAchange*	*AnnoExon*
ALK	052448	3	2	2	29445412	exonic	NM_004304	nonsynonymous SNV	G3421A	D1141N	21
ANKRD17	012081	3	1	4	73956974	exonic	NM_198889	nonsynonymous SNV	A5618G	Q1873R	28
APC2	012081	3	1	19	1469322	exonic	NM_005883	nonsynonymous SNV	C6022G	R2008G	15
ARID3A	052448	3	2	19	966658	exonic	NM_005224	nonsynonymous SNV	G1285A	A429T	7
ARID4B	052448	3	1	1	235377278	exonic	NM_001206794	nonframeshift substitution	1630_1647GAGGAGGAGGAGGAA		17
ASXL1	007178	3	1	20	31022277	exonic	NM_015338	stopgain	C1762T	Q588X	12
ASXL2	052448	3	1	2	25990590	exonic	NM_018263	nonsynonymous SNV	T637C	W213R	7
BARD1	012081	3	1	2	215645906	exonic	NM_001282543	nonsynonymous SNV	C635T	S212F	3
CHEK1	010482	5	1	11	125497644	exonic	NM_001114121	nonsynonymous SNV	T208A	F70I	3
DCC	013049	4	2	18	50942526	exonic	NM_005215	nonsynonymous SNV	G3163A	G1055S	21
DCC	051656	3	2	18	51013178	exonic	NM_005215	nonsynonymous SNV	G3748A	A1250T	26
DGKB	052448	3	2	7	14775696	exonic	NM_004080	nonsynonymous SNV	G292A	V98I	4
ERBB4	051656	3	1	2	212285326	exonic	NM_001042599	nonsynonymous SNV	G2975A	R992H	25
ERCC3	051656	3	2	2	128038128	exonic	NM_000122	frameshift substitution	1421_1422AAT		9
ERCC8	012828	4	2	5	60186885	exonic	NM_001290285	nonsynonymous SNV	G413A	S138N	9
GLI2	010482	5	2	2	121742233	exonic	NM_005270	nonsynonymous SNV	G1870A	G624S	11
GNAS	013049	4	1	20	57429643	exonic	NM_001077490	nonsynonymous SNV	C1136T	P379L	1
JAK2	052448	3	1	9	5054748	exonic	NM_004972	nonsynonymous SNV	C800G	T267R	7
JAK2	052448	3	1	9	5089773	exonic	NM_004972	nonsynonymous SNV	C2671T	H891Y	20
MAP3K1	013049	4	1	5	56111817	exonic	NM_005921	nonsynonymous DNV	417_418GT	AA139_140AS	1
MAP3K13	012828	4	1	3	185190894	exonic	NM_001242317	nonsynonymous SNV	G1154A	R385Q	10
MAP3K4	012081	3	1	6	161512562	exonic	NM_001291958	nonsynonymous SNV	T1484C	F495S	13
MLH3	052448	3	2	14	75508329	exonic	NM_001040108	nonsynonymous SNV	C3454T	R1152C	4
NF1	050904	4	3	17	29653223	exonic	NM_000267	nonsynonymous SNV	C5158A	H1720N	36
PALB2	012081	3	1	16	23646663	exonic	NM_024675	nonsynonymous SNV	C1204G	L402V	4

POLE	013049	4	1	12	133253953	exonic	NM_006231	nonsynonymous SNV	G797A	R266Q	8
RAD52	013049	4	1	12	1023614	exonic	NM_001297421	nonsynonymous SNV	T719G	V240G	8
RBL1	051656	3	1	20	35635933	exonic	NM_002895	nonsynonymous SNV	T2752C	C918R	20
ROS1	013049	4	2	6	117710981	exonic	NM_002944	nonsynonymous SNV	A1291G	I431V	12
SLX4	012081	3	1	16	3640775	exonic	NM_032444	nonsynonymous SNV	A2864C	H955P	12
SLX4	050904	4	1	16	3652140	exonic	NM_032444	nonsynonymous SNV	G929A	R310Q	4
TBX2	012828	4	1	17	59483090	exonic	NM_005994	nonsynonymous SNV	G1579A	G527R	6
TET2	013049	4	1	4	106156675	exonic	NM_001127208	stopgain	C1576T	Q526X	3

N fam: number of individuals in the family. N seq: number of individuals sequenced. N var: number of variants identified in data set. Chr: chromosome. AnnoRegion: Genomic region as annotated by annovar. AnnoRefSeq: efSeq ID as annotated by annovar. AnnoType: Effect of mutation such as synonymous, nonsynonymous. AnnoNTchange: Nucleotide base change, AnnoAAchange: Amino Acid Change, AnnoExon: Exon number in transcript, SNV: single nucleotide variant.

Appendix C: Rare segregating variants

AnnoGene	*Family*	*N fam*	*N var*	*chr*	*position*	*AnnoRegion*	*AnnoRefSeq*	*AnnoType*	*AnnoNTchange*	*AnnoAAchange*	*AnnoExon*
ABCB5	050904	4	4	7	20691041	splicing					
EDNRB	007178	3	3	13	78492540	exonic	NM_001122659	nonsynonymous SNV	G169A	G57S	1
ERBB3	007178	3	3	12	56495397	exonic	NM_001982	nonsynonymous SNV	A3587G	E1196G	28
FANCI	051656	3	3	15	89811698	exonic	NM_001113378	nonsynonymous SNV	T824C	I275T	10
KDM1B	051656	3	3	6	18197821	exonic	NM_153042	nonsynonymous SNV	T754C	S252P	10
MAP3K6	007178	3	3	1	27688743	splicing					
MUTYH	050904	4	4	1	45797228	exonic	NM_001048171	nonsynonymous SNV	G1145A	G382D	13
PML	051656	3	3	15	74327949	exonic	NM_033250	nonsynonymous SNV	A2003G	Q668R	7
SLK	051656	3	3	10	105765430	exonic	NM_014720	nonsynonymous SNV	G2461A	E821K	10
TYRP1	052448	3	3	9	12694066	exonic	NM_000550	nonsynonymous SNV	G70A	A24T	2
TYRP1	052448	3	3	9	12695586	exonic	NM_000550	nonsynonymous SNV	C457T	R153C	3
WWOX	051656	3	3	16	78149000	exonic	NM_001291997	nonsynonymous SNV	C19T	R7W	3
MAP3K11	010482_4	5	4	11	65365787	exonic	NM_002419	nonsynonymous SNV	C2519T	P840L	10
CKAP2	010482_3	5	3	13	53047966	exonic	NM_001098525	nonsynonymous SNV	G1552A	E518K	8
HUS1	010482_3	5	3	7	48004991	exonic	NM_004507	nonsynonymous SNV	G805A	D269N	8

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Appendix D: Rare non-segregating variants

AnnoGene	*Family*	*N fam*	*N var*	*chr*	*position*	*AnnoRegion*	*AnnoRefSeq*	*AnnoType*	*AnnoNTchange*	*AnnoAAchange*	*AnnoExon*
APC	007178	3	2	5	112102960	exonic	NM_001127511	nonsynonymous SNV	C325T	R109W	3
APC	010482	5	2	5	112179153	exonic	NM_001127511	nonsynonymous SNV	C7808G	S2603C	14
ARID3A	007178	3	2	19	971974	exonic	NM_005224	nonsynonymous SNV	G1691A	R564Q	9
ARID4A	012828	4	2	14	58832019	splicing					
ARID5A	012081	3	2	2	97216846	exonic	NM_212481	nonsynonymous SNV	G581A	G194E	7
AXIN1	010482	5	1	16	348021	exonic	NM_003502	nonsynonymous SNV	C1485G	D495E	6
AXIN2	012081	3	1	17	63532594	exonic	NM_004655	nonsynonymous SNV	T1985C	L662P	8
BRCA1	007178	3	1	17	41243509	exonic	NM_007297	nonsynonymous SNV	A3898G	R1300G	9
BRCA1	051656	3	1	17	41226488	exonic	NM_007297	nonsynonymous SNV	G4394T	S1465I	13
BRCA1	013049	4	1	17	41243840	exonic		nonsynonymous SNV		N1189K	9
BRCA2	013049	4	2	13	32953550	exonic		nonsynonymous SNV		A2951T	10
BRCA2	013049	4	1	13	32906766	exonic		nonsynonymous SNV		C1151T	22
BRCA2	007178	3	1	13	32972626	exonic	NM_000059	stopgain	A9976T	K3326X	27
BRIP1	010482_4	5	3	17	59924512	exonic	NM_032043	nonsynonymous SNV	G577A	V193I	6
BRIP1	012828	4	2	17	59924572	exonic	NM_032043	nonsynonymous SNV	C517T	R173C	6
BUB1	051656	3	2	2	111425226	exonic	NM_001278616	nonsynonymous SNV	C617T	A206V	7
CDKN2A	050904	4	3	9	21974640	exonic	NM_058197	nonsynonymous SNV	G187C	G63R	1
DNMT3B	012081	3	1	20	31386313	exonic	NM_001207056	nonsynonymous SNV	C1250T	A417V	12
FANCI	013049	4	1	15	89856189	exonic	NM_018193	nonsynonymous SNV	G3526A	V1176I	34
MAP3K12	050904	4	3	12	53876569	exonic	NM_001193511	nonsynonymous SNV	G2018A	G673D	11
MAP3K6	007178	3	3	1	27688743	splicing					
MC1R	007178	3	2	16	89986091	exonic	NM_002386	nonsynonymous SNV	G425A	R142H	1
MLH1	012081	3	2	3	37092019	exonic	NM_001258271	nonsynonymous SNV	G1939A	V647M	17
MSH6	010482_3	5	2	2	48026308	exonic	NM_001281492	nonsynonymous SNV	C796G	L266V	2
SOX13	013049	4	2	1	204092087	exonic	NM_005686	nonsynonymous SNV	G1130A	R377H	10

SOX4	013049	4	1	6	21594847	exonic	NM_003107	nonsynonymous SNV	C82G	L28V	1
TERT	012081	3	1	5	1272311	exonic	NM_001193376	nonsynonymous SNV	G2371A	V791I	7
TP53BP2	050904	4	2	1	224001984	exonic	NM_001031685	nonsynonymous SNV	C247T	R83C	3
WWOX	013049	4	1	16	78466409	exonic	NM_001291997	nonsynonymous SNV	G477T	L159F	7
XRCC4	050904	4	3	5	82406931	exonic	NM_003401	nonsynonymous SNV	T224C	L75S	3

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